The New England
Journal of Medicine

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Volume 252 JANUARY 6, 1955 Number 1

# RADIOACTIVE ISOTOPES AS AIDS IN MEDICAL DIAGNOSIS*

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NEW YORK CITY

I AM very much honored by the invitation to deliver the George Holmes Lecture this year. It is a privilege and a pleasure to join in paying tribute to an outstanding leader.

A long time ago I knew Dr. Holmes as one of the leading lights in American radiology; I respected his position and admired his wide knowledge in the field. Then I came to know him personally, and to my respect and admiration were added real affection for a comfortable friend. He occupies for me — and I am sure for many others — a unique position.

Dr. Holmes's great fields were teaching and diagnostic radiology. The latter, for him, meant mainly the interpretation of radiographic and fluoroscopic examinations, with constant development of methods for getting more information out of such examinations. The advent of radioactive isotopes into the field of medical diagnosis came only in very recent years, just about the time Dr. Holmes was withdrawing from his general work. I am sure that, given a little more time, he would have become involved in the use of this newer procedure for radiologic diagnosis.

## GENERAL CONSIDERATIONS

Radioactive isotopes are chemically identical with their stable counterparts. They behave in the same way in chemical reactions, and are handled in the same manner by physiologic and metabolic processes. But their atoms possess the unique property of disintegrating, and emitting radiation in the act, which makes it possible to follow them through all sorts of procedures and reactions. In following them, it is also possible to trace the paths of their nonradioactive twins.

The rate of disintegration of these substances is commonly expressed by a statement of their *half lives*. The half life is the period in which half of all the atoms of the particular isotope present will have disintegrated; in the next half period half the remainder will go, and so on. Thus, about seven half lives are necessary to reduce any given amount of an isotope to 1 per cent of its initial value. Half lives of various isotopes range from fractions of a second to millions of years; for those useful in medicine, for the most part, half lives vary between a few hours and a few weeks. Radioactive potassium ($K^{42}$) has a half life of 12.4 hours; its period for reduction to 1 per cent is about 3.5 days. Radioactive phosphorus ($P^{32}$) with a half life of 14.3 days, will not be reduced to 1 per cent until over three months have elapsed.

The amount of any radioactive isotope is expressed in terms of curies, or millicuries or microcuries, the last being the normal one for diagnostic procedures. A microcurie of any isotope is that quantity in which 37,000 atoms disintegrate per second. If an isotope has a long half life, a microcurie of it will have to contain more atoms than if it has a short one, to keep up the supply for disintegration. Of course, as the amount decreases by this disintegration, what was originally a microcurie becomes less, but the reservoir has to keep up the supply for whatever the natural rate may be.

An isotope with a half life of 8 days, such as radioactive iodine ($I^{131}$), contains about 37,000,000,000 atoms per microcurie. This sounds like a large number of atoms, but it is a very small part of a microgram, — about one one-hundred-thousandth. Some radioactive isotopes can be obtained in such a form that every atom of the element in question is radioactive; in this case the preparation is said to be "carrier free." $I^{131}$ is one of these; the actual weight of iodine in a dose of the material administered for any diagnostic purpose would be almost infinitesimal. Other isotopes can be obtained only in a mixture with stable isotopes of the same element; in this case they are said to be "with carrier," and the specific activity is the total amount of the isotope per gram of element. For instance, radioactive sodium ($Na^{24}$) is supplied by the Oak Ridge National Laboratory with a specific activity of 90 mc. per gram of sodium. This means that a dose of this material would contain about a million times as much stable as radioactive sodium.

Radioactive isotopes emit beta or gamma radiation, or both. (Only a very few artificially made radioactive isotopes emit alpha particles, and these need not be considered here.) The beta rays may be so

*The George Holmes Lecture, presented at a meeting of the New England Roentgen Ray Society, Boston, May 22, 1953.

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unpenetrating that a small fraction of a millimeter of tissue will stop them all, as in radioactive carbon and sulfur, or they may traverse several millimeters, as those from radioactive phosphorus do. The most penetrating beta rays known to be emitted by a radioactive isotope with a half life of more than a few minutes are those from radioactive potassium, with a maximum range in tissue of nearly 2 cm. Gamma-ray energies range from less than 100 kv. in radioactive iron, to more than 2,000,000 volts in radioactive sodium.

It is evident that both the lifetime and the kind of radiation emitted by an isotope will be important considerations in the types of investigation that can be made with it. Obviously, a study extending over several days cannot be made with an isotope having a half life of a few minutes. It is a great misfortune that all 3 radioactive isotopes of oxygen have half lives less than 3 minutes, and those of nitrogen 10 minutes or less. Furthermore, if it is desired to observe concentration of the material in an organ in a living body, the radiation emitted must be sufficiently penetrating to reach external measuring instruments. It would not be possible to measure concentration of a carbon compound in the liver in the living human being by means of the 150 kv. beta rays from Carbon-14.

Two other limitations exist on tests to be performed with radioactive isotopes; these may be called the avoidance of chemical effect and avoidance of radiation effect. Chemical effect would never result if carrier-free isotopes were used. With carrier present, a relatively large amount of the stable isotope may alter the physiologic situation. This is best illustrated by studies with radioactive iodine in the thyroid gland. In the normal person about a third of a dose of carrier-free radioactive iodine will concentrate in the thyroid gland within 24 hours. But if a few milligrams of stable iodine are used as carrier, the uptake is appreciably lowered. The normal daily intake of iodine by the adult human being is about 100 to 200 microgm. and normal thyroid function is based on this. The larger dose floods the gland with iodine, and upsets the normal procedure. This is discussed below in more detail.

Radiation effect would result if the radiation emitted by the test dose of the radioactive material were sufficient to bring about physiologic changes that might affect the reaction being tested. This will seldom, if ever, occur in the human being at present. Most test doses are planned to deliver not more than 0.3 r to the patient in the first week, and less in any subsequent one; this is assumed to be the permissible dose that will have no detectable effects. In animal experimentation, in which considerably larger doses may be employed, the question might arise. For instance, 1 mc. of $P^{32}$ in a 20-kg. dog would deliver a whole-body dose of about 40 rep. (roentgen equivalent, physical) and this might be enough to bring about metabolic changes that would interfere with study of some metabolic processes.

Various types of studies with radioactive isotopes are useful as diagnostic aids. This is a different thing from saying that they are "diagnostic tests." Actually, there are in medical practice very few truly diagnostic tests that reveal that the patient does or does not have a certain disease or condition. The Wassermann and Aschheim–Zondek are, of course, two that come immediately to mind. At present no test with an isotope is in this class, although some of them may be before very long.

The biologic or physical studies that can be made with radioactive isotopes cover a wide range of phenomena, such as uptake, distribution and excretion of an element, turnover rates in particular tissues and the nature of the products of intermediary metabolism, which as yet have little or no direct significance as diagnostic aids. However, most of the studies now used clinically started as pieces of physiologic research. It is probable that others will cross the line from the purely investigative to the practical.

Useful studies as aids in medical procedures are based on one of four phenomena: the dilution of a known amount of isotope, to determine the volume of the diluting fluid; the rate of transfer from one part of the vascular system to another, to ascertain some fact about the circulation; the rate of disappearance of an isotope that has been injected directly into a certain tissue, to reveal the state of the local circulation in that tissue; and the concentration of the isotope in a particular organ or tissue, to determine something about the local function of that tissue.

## Dilution Studies

Examples of dilution studies are determinations of the volume of blood, plasma, red cells and extracellular fluid. The basic procedure is the same in all cases. A known amount of the isotope to be used is injected into the circulation. After an appropriate time for mixing into the fluid studied, a blood sample is taken and the dilution determined.

The most frequently used isotope for blood-volume determinations at present is radioactive iodine, used as a tag or label for human serum albumin.* This is a large protein molecule that does not pass readily out of the capillaries, and the iodine atom is firmly incorporated into the molecule. Hence dilution of this substance should measure the same volume as the blue dye commonly used. This has been shown to be so, and the radioactive procedure is simpler and faster. The steps are outlined in Table 1. Since the albumin is all in the plasma, the plasma volume can be obtained by centrifugation and measurement directly, or from the hematocrit. If, instead of whole blood, the sample had been centrifuged and only the plasma measured, the counts per cubic centimeter would

*This lecture was delivered before radioactive chromium became widely employed for blood-volume studies.

have been 545, and the dilution factor would have been 2750, giving plasma volume directly. Whole-blood volume and cell volume would then have been obtained from the hematocrit.

One great advantage of this test is that it can be repeated as often as need be within a brief period. In surgical procedures, when blood loss may be serious and the question of transfusion arises, a second or later test can be done at any time. It is only necessary to take a blood sample before administration of the dose, to correct for radioactivity already present from the first test. The procedure is shown in Table 2, assuming the determination in Table 1 to have been preoperative.

If for any reason it is desired to make actual measurements of cells and plasma separately, rather than rely on the hematocrit, the cells can be labeled directly with radioactive phosphorus or potassium. In this case a heparinized blood sample has to be taken from the person to be studied, and the cells suspended in a solution containing the isotope and incubated with this for about two hours at body temperature. The cells are then washed and resuspended in sterile saline solution; the injection and dilution procedure is the same as with the previous example. Whole-blood volume is obtained directly in the same manner, but

TABLE 1. *Measurement of Blood Volume Using Radioactive-Iodine-Labeled Human Serum Albumin (I-HSA).*

| PROCEDURE | BLOOD VOLUME |
|---|---|
| 50 microcuries $I^{131}$ injected in 5 cc. of saline solution | |
| Counts/microcurie/min. | 30,000 |
| Counts for 50 microcuries would be | 1,500,000 |
| After 5 min. blood taken | |
| Counts for 5 cc. of whole blood | 1,500 |
| For 1 cc. counts would be | 300 |
| Dilution factor: $\frac{1,500,000}{300} = 5000$, indicating 5000 cc. of whole blood. | |
| With hematocrit of 0.45: | |
| Red-cell volume | 2,250 cc. |
| Plasma volume | 2,750 cc. |

all the radioactivity is in the cells, which can be measured directly after centrifugation.

Whole-blood volume evaluated by tagged-albumin dilution is always about 8 per cent greater than that derived from dilution of tagged erythrocytes. This is not because of errors in methods, but probably because of differences in the rate of mixing and in the pools into which mixing takes place. If one method is used consistently, this difference is insignificant. For repeated studies, the serum albumin is probably to be preferred to any other method.

In cases of excess fluid formation, such as ascites or edema, it may be desirable to know whether the rate of production of the fluid, or its total amount, is changing. Of course, visual and symptomatic observations are useful, but a measure of the so-called "extracellular fluid" may also be desirable. This is also done by a dilution technic, as with blood volume. However, the indicator used must be one that passes readily from the capillaries to the extravascular fluid; it should furthermore be one that does not readily enter into cells. Various chemicals are employed, such as thiocyanate and sucrose. Isotopes used are sodium, bromine, chlorine and others, in simple inorganic compounds. The material is injected, time is allowed for equilibration in extravascular fluid, and the dilution factor is determined. All these elements do enter cells to a certain degree, so that what is measured is more properly called "sodium space," "bromide space" and so on. However, repeated measurements with the same isotope, and the same mixing

TABLE 2. *Repeat Measurement of Blood Volume.*

| PROCEDURE | | BLOOD VOLUME |
|---|---|---|
| | | *count/min./cc. of blood* |
| Before 2d injection | | 300 |
| 50 microcuries injected 2d time (additional counts) | | 1,500,000 |
| Sample taken 5 min. later | | 750 |
| Counts due to 2d dose | 750 − 300 = | 450 |
| Dilution factor: $\frac{1,500,000}{450} = 3325$, indicating blood volume of 3325 cc. | | |
| Blood loss | 5000 − 3325 = | 1,675 cc. |

time, should indicate shifts in the space under consideration, and if this can be shown to be due only to accumulation or disappearance of fluid, the desired information is obtained. It should be noted that although adequate mixing in the normal person may occur in an hour or so, a considerably longer period may be necessary when massive fluid accumulation is present.

## RATE OF TRANSFER

Studies based on rate of transfer are fundamentally illustrated by the determination of circulation time. An isotope can be injected into a definite place in the vascular system, rapidly and in a small volume of solution; its arrival at another place is observed by a detector located there. Time elapsed between injection and detection is circulation time between the two points. A study based on such measurements was made by a group in England, who were concerned with venous flow in the lower extremities in women in labor and during the puerperium.[1] The frequency of edema and varicose veins in these cases suggested that venous flow was impeded by pressure of the gravid uterus on the veins in the pelvis; this the authors wished to investigate. A small amount of radioactive sodium in physiologic saline solution was injected in a vein at the dorsum of the foot, and the time of its arrival at the femoral vein recorded.

Figure 1 gives results in a group of normal women and in a group tested both during labor and shortly

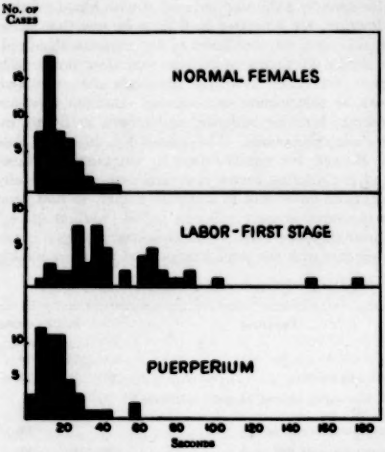


FIGURE 1. *Changes in Foot-to-Groin Circulation Time Late in Pregnancy and in the Puerperium, As Determined by Means of Radioactive Sodium (Reproduced from Wright, Osborne and Edmonds[1] with the Permission of the Publishers).*

post partum. It is quite apparent that in the second group there was a definite slowing of circulation at the end of pregnancy that was quickly relieved after delivery.

A more elaborate procedure of the same type[2] has been developed as the so-called "radiocardiography." Here, the radioactive sodium is injected into an antecubital vein, and its passage through the heart and lungs followed by a Geiger counter and recorded. Figure 2 presents the radiocardiogram for a normal person. The tracing reads from left to right, the vertical lines being spaced at one-second intervals. The R wave represents blood going into and leaving the right side of the heart; the T region is while it is in the lungs, and the L wave shows passage into and out of the left side of the heart. The whole procedure takes only a few seconds. The upper part of Figure 3 gives the tracing for a patient with patent ductus arteriosus; the lower one is for the same patient after operation. Charts of this sort may well take their place with electrocardiograms, after the method has been perfected.

Studies of peripheral circulation can be carried out with various isotopes. The material is injected into the blood stream in the arm, if circulation is to be studied in the foot. If a large molecule, such as iodine-labeled albumin, is employed, it will remain in the vascular system. Activity measured against the foot (Figure 4) indicates the rate at which the isotope comes into equilibrium with normal plasma in the capillaries, and therefore represents the manner in which the capillary plexus may be cleared.[3] Figure 5 shows such a curve for a normal foot and for one that has been kept cold.

If, instead of a large molecule, an ion is used that escapes readily into the extravascular space, such as the sodium in sodium chloride, the build-up takes longer but gives information about the condition not

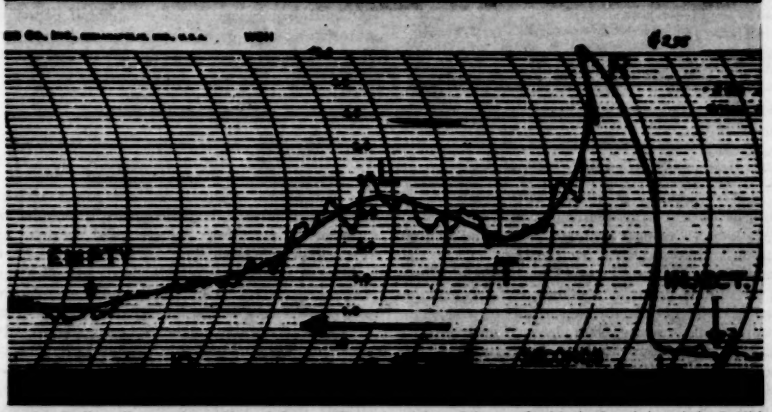

FIGURE 2. *Radiocardiogram for a Normal Person (Reproduced from Prinzmetal[2] with the Permission of the Publishers).*

only of the capillaries, but also of the capillary bed. The general picture for normal persons and for patients afflicted with scleroderma and with Raynaud's disease is presented in Figure 6. Late in the war such studies were made in men who had been shipwrecked and had passed days exposed in open boats, presenting the condition known as immersion foot. At the time of these tests their feet appeared normal, but the men complained of severe pain on standing or in the cold. From the curves (Fig. 7) it is obvious that their general capillary picture was subnormal. One of these men had been accused of malingering and penalized for it; on the basis of the isotope findings he was exonerated.

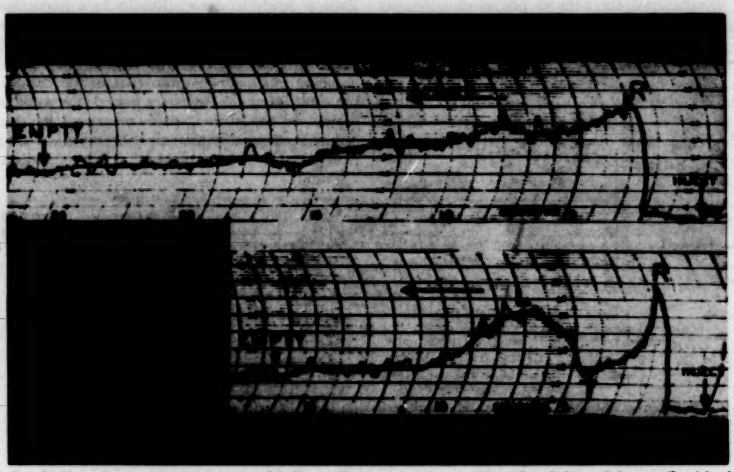


FIGURE 3. *Radiocardiograms for a Patient with Patent Ductus Arteriosus (Reproduced from Prinzmetal[2] with the Permission of the Publishers).*

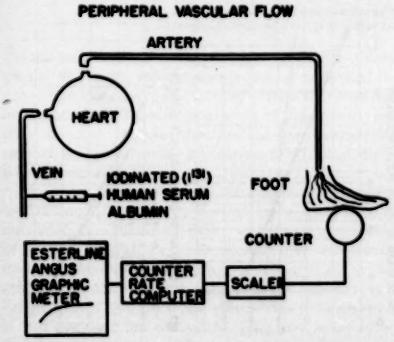


FIGURE 4. *Diagram of Setup for Study of Peripheral Circulation with Radioactive Isotope (Reproduced from MacIntyre et al.[3] with the Permission of the Publishers).*

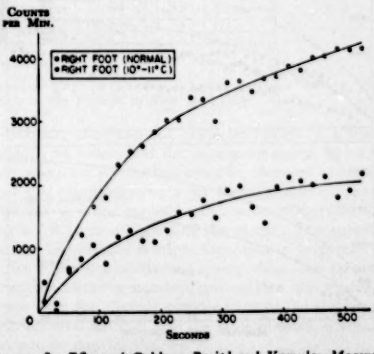


FIGURE 5. *Effect of Cold on Peripheral Vascular Measurement with Radioactive-Iodine-Labeled Human Serum Albumin (Reproduced from MacIntyre et al.[3] with the Permission of the Publishers).*

## RATE OF DISAPPEARANCE

Studies of rate of disappearance of isotope from a tissue[4] offer a different index of circulation — one dealing with the actual nourishment of a small frag-

ment of tissue under observation. The isotope, in a very small volume, is injected directly into the tissue under investigation, the counter placed directly over

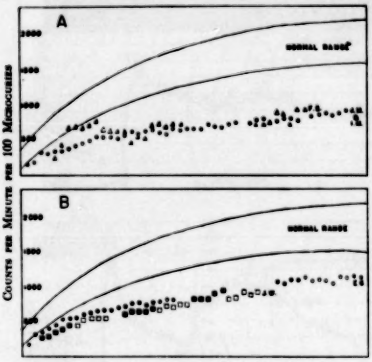


FIGURE 6. *Build-up of Radioactive Sodium in the Intravascular and Extravascular Spaces in the Foot in Normal Persons and in Patients with Scleroderma or Raynaud's Disease.*

it, and the disappearance rate observed (Fig. 8). This procedure is of value in tests of circulation in

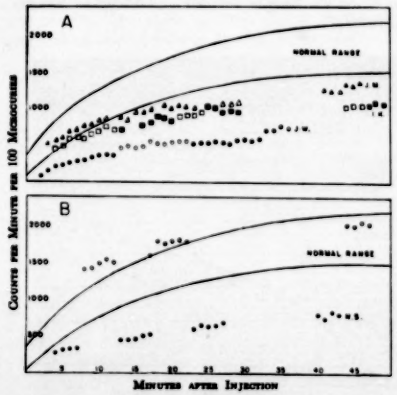


FIGURE 7. *Effect of Immersion Foot on Radiosodium Build-up.*

tubed pedicles used in grafts in plastic surgery. The moving of such a flap is possible only when it has adequate circulation. Sometimes, movement from the initial to the final site requires repeated stages, with sufficient time for circulation to be established at each stage. Too early transplantation leads to failure of the graft to grow. By use of radiosodium clearance tests, the circulation from a site on the graft and from a control site is compared. When they are equal, the graft is ready to move. Results in a particular case from the Bronx Veterans Administration Hospital[5] are presented in Figure 9. The left-hand graph shows circulation in the graft as it was first established as being much slower than that in the control. On the right, after the necessary period, the rates are the same, and the graft is ready to move. By this procedure considerable time may be saved as compared with the conservative waiting period generally used.

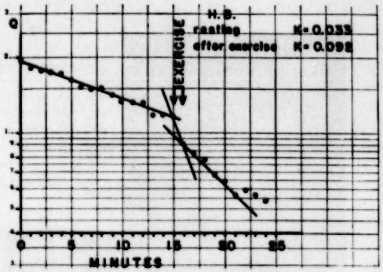


FIGURE 8. *Clearance of Radiosodium from Muscle Tissue (Reproduced from Wisham and Yalow[4] with the Permission of the Publishers).*

## CONCENTRATION

Concentration of an isotope in a particular tissue, for study of some function of that tissue, is best typified by studies of thyroid function with radioactive iodine. Inorganic iodine taken into the body is either

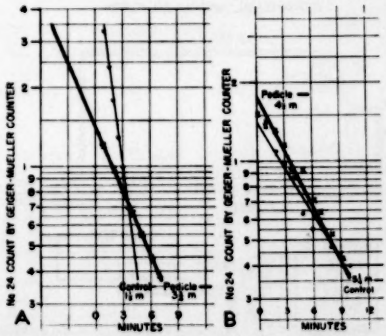


FIGURE 9. *Clearance of Radiosodium from a Tubed Pedicle Graft (Reproduced from Conway et al.[5] with the Permission of the Publishers).*

deposited in the thyroid gland or promptly eliminated by way of the kidneys. In the gland it is elab-

orated into thyroid hormone and discharged again into the circulation. It is evident that several different phenomena can be studied as indications of thyroid function. These include measurement of the rate of deposition of iodine in the gland in vivo, the total accumulation in a specified period or the output of organic iodine in the blood as hormone. Any of these shows higher values in hyperfunction than in normal function and lower values in hypofunction. Measurement of kidney excretion is also an indication of gland from functioning normally. It is necessary to withdraw medication with iodine or thyroid hormone for some weeks before the results of any of these studies can be accepted as valid; the severe overdose of iodine due to x-ray dyes may inhibit proper function for a few months.

The simplest test of thyroid function by $I^{131}$ uptake is the direct determination of the part of the administered dose that is collected in the thyroid gland at some definite number of hours after administration.

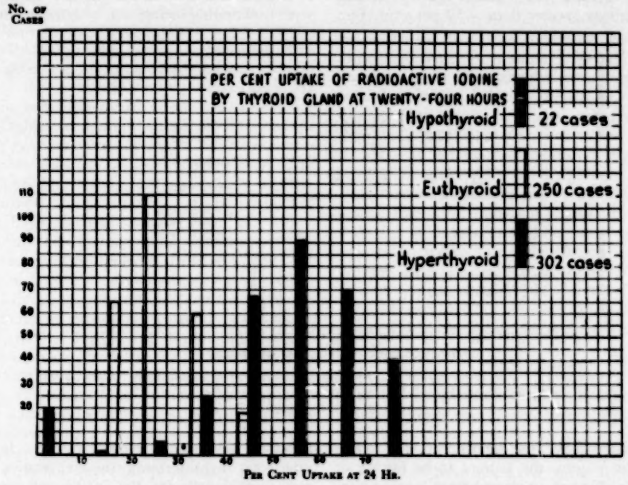


FIGURE 10. *Twenty-Four-Hour Radioiodine Uptake in Thyroid Gland in a Series of Hypothyroid, Euthyroid and Hyperthyroid Subjects in the Vicinity of New York City.*

the amount that has *not* been taken up by the thyroid gland, but such measurements are complicated by any variations in renal function. None of these tests are affected by the emotional state of the patient, and they do not require the preliminary preparation needed for an accurate measurement of basal metabolic function.

However, before the result of any tests with radioiodine can be accepted, it must be assured that no chemical complications exist, and there are several of them. It must be remembered that the normal daily intake of stable iodine is about 100 to 200 microgm. Administration of an amount appreciably in excess of this will flood the gland with iodine so that it will not function normally. This may occur either from treatment with iodides, or with medicines containing them, such as some cough syrups, from x-ray studies with certain opaque dyes or even from painting of the skin with iodine for purposes of asepsis. Previous therapy with desiccated thyroid or with antithyroid drugs such as thiouracil also prevents the

The tracer dose may be given by mouth in a small quantity of water, and the uptake measured 24 hours later. Certain precautions must be observed to ensure that the counting tube is far enough from the neck and has a large enough window so that radiation reaches it from all parts of the gland. The support for the Geiger tube is adjustable and can be placed at a fixed distance above the neck. Also, the counter must be correctly standardized so that the readings made over the thyroid gland and over the sample of administered solution give the same number of counts per minute per microcurie.

The results of such measurements on a series of normal persons and on hyperthyroid and hypothyroid patients, made in New York City, are shown in Figure 10. In patients with hypofunction the uptake at 24 hours is 0 to 10 per cent of the administered dose, when correction is made for radioactive decay; it is 10 to 45 per cent in euthyroid subjects and 30 to 90 per cent in hyperthyroid persons. It is immediately apparent that although there is adequate separation

between hypothyroid and normal persons, there is a certain overlap between normal and hyperthyroid subjects. If 40 per cent is accepted as the dividing point, 6 per cent of the normal persons have greater uptake, and 10 per cent of the hyperthyroid patients have less. This is an improvement over the results of measurement of basal metabolic rate, as shown by studies on a series of 175 patients subjected to both tests at the same time. If the normal basal metabolic rate is assumed to be between −10 and +10 per cent, 15 per cent of normal persons had readings below −10 and 7 per cent readings greater than +10 per cent. Furthermore, as stated above, the determination of iodine uptake does not require the patient to be fasting or at rest, and the effect of emotional state is greatly reduced.

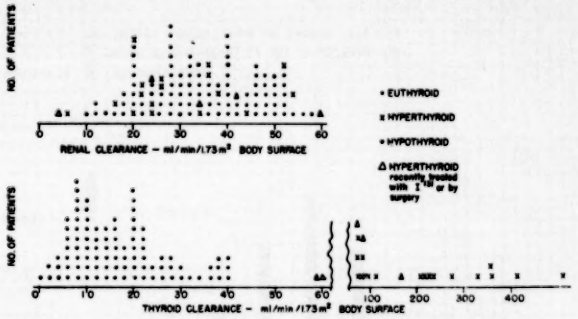


FIGURE 11. *Values for Renal and Thyroid Clearances of Radioiodine in Hypothyroid, Euthyroid and Hyperthyroid Persons (Reproduced from Berson et al.[4] with the Permission of the Publishers).*

In a large group of cases, then, this simple test gives satisfactory data in about 85 per cent; it fails in between 10 and 15 per cent, and these are likely to be the cases that are also clinically indeterminate. It should be pointed out that since clinically all grades of differentiation between the normal and the toxic state exist, it may not be possible for a physiologic test of this sort to separate them completely. However, more elaborate tests have been devised for aid in these cases. The measurement of thyroid clearance as devised by the group at the Bronx Veterans Administration hospital[6] is perhaps the most satisfactory. The procedure involves intravenous injection of the radioiodine, constant counting over the thyroid gland for half an hour and the taking of a urine specimen at the end of this period. The plasma concentration is estimated on the basis of an average "iodide space" calculated from body weight; all iodine not deposited in the thyroid gland or eliminated by the kidneys is assumed to be uniformly distributed in this space. The observed values are put into a set of formulas that give thyroid and renal clearances during the first half-hour period. The investigators found no difference in the rates of renal clearance during this period for different states of the thyroid gland, but striking differences in those of thyroid clearances between the euthyroid and the hyperthyroid group (Fig. 11).

Iodine will localize in functioning thyroid tissue anywhere. Accordingly, it is readily possible to find the position of aberrant thyroid tissue. This has been particularly useful in differentiating substernal thyroid gland and mediastinal tumor. In thyroid cancer with functioning metastases, such metastases can sometimes be located. In general this can be done only after total thyroidectomy; the competition of the normal thyroid cells for the iodine will result in very small uptake in metastases.

A rather amusing use of this isotope has been in the detection of factitious thyrotoxicosis. The clinical picture of self-induced hyperthyroidism may be indistinguishable from that of spontaneous thyrotoxicosis. The condition sometimes arises from excessive self-medication in the effort to reduce weight; these patients will usually admit it and can be persuaded to stop the medication, when the diagnosis can be made on correction of symptoms. However, patients with psychiatric problems may not admit that they are taking thyroid, and will go to considerable lengths to conceal it. If the condition is suspected, a test of iodine uptake should be done. The true hyperthyroid patient will show a high uptake, whereas one with toxic symptoms induced by thyroid medication will have no uptake whatever.

It has always been hoped that radioactive tracers could be found that would definitely identify cancerous tissue. Unfortunately, up to the present time this hope has not been borne out. However, it is true that any tissue that is metabolizing rapidly will show earlier or higher uptake of any metabolite than cor-

responding normal tissue. This phenomenon has been utilized in the attempt to localize tumors not readily demonstrable otherwise.

Most popular of these has been the localization of brain tumors. The surgeon is anxious for help of this sort. In general the blood-brain barrier inhibits the rapid entrance of nonphysiologic material into the central-nervous-system tissues. However, in the presence of inflammation or of a neoplastic growth, this barrier (whose exact nature is unknown) is disrupted and allows the tracer to flood the region. The mechanism whereby more of the isotope is concentrated in the tumor than in the normal tissue is not known, but the concentration does occur. Localization then depends on counting at symmetrically located sites on both sides of the head and finding where there are differences in level. At present the tracer of choice is radioactive iodinated human serum albumin, which gives rather high differentials, with tissue levels remaining stable for two or three days. Very small tumors and midline tumors are not readily located, but some clinical groups report a high percentage of successes in large series of cases.

Recently, procedures have been developed to detect silent metastases in the liver, which are one of the chief causes of failure in surgical treatment of cancer. The various liver-function tests and needle biopsy are the only laboratory procedures currently available to the clinician for the detection of such metastases, and they are notoriously unreliable when one is dealing with small, solitary or early growths. However, these are frequently demonstrated by administration of a radioactive tracer and counting of points in a pattern over the region. The tracer employed by the group at the Los Angeles Veterans Administration Hospital, who first reported on this procedure, is iodine-labeled human serum albumin. The tracer dose is administered intravenously and the patient studied 24 hours later. Counting over a 5-cm.-square lattice pattern is sufficient to show regions of increased uptake. Very small or deep-seated masses may be masked by normal liver. Nevertheless, in a series of 151 patients studied by the group just mentioned, an over-all accuracy of 95 per cent was obtained. In 32 patients found at operation to have metastases, 30 had previously been designated as positive by radioactive survey. Of 119 grossly normal, 114 had been within the control range for the isotope test. Since preoperative knowledge of the existence of liver metastases would be extremely valuable, it appears that this test should have wide use.

Efforts have been made to find a bone-seeking isotope that could be used as a detector of bone metastases. Some success has been achieved with radioactive gallium; however, this isotope also shows deposit in arthritic areas. In general these metastases can be found by means of x-ray examination as soon as by an isotope tracer.

## Discussion

Other tests and studies could be discussed, but the foregoing, at present, have been found most useful.

No discussion of diagnostic uses of isotopes would be complete without mention of dosage levels and radiation safety. The International Commission of Radiological Protection has set 0.3 r measured in air, or 0.5 r to the entire body, as the maximum permissible level for the weekly dose of radiation for occupational exposure. In establishing dosage levels for diagnostic tests, an effort is usually made to keep whole-body radiation, or radiation to any critical tissue, below this level. Nevertheless, just as the radiologist does not hesitate to exceed this for diagnostic purposes, when the patient is expected to derive some benefit from the procedure, so, when justified, isotope doses can be somewhat increased. Constantly improving instrumentation has served in many cases to make it possible to use lower doses than those originally considered necessary. None of the tests discussed above should result in administration of an undue amount of radiation to any patient.

As far as danger to anyone else is concerned, with any test or tracer dose of any isotope likely to be employed, there is absolutely no hazard either from the patient himself or from his excreta. No precautions need be observed. These are solely for therapeutic doses, which are outside the scope of this discussion.

## Conclusions

It may be said that various procedures with radioactive isotopes are valuable as diagnostic aids. If it is thought that progress has been slow, and that these substances — from which I am afraid miracles were expected — have not lived up to all that was hoped from them, it should be remembered that it is just twenty years since artificial radioactivity was discovered and that isotopes have not been generally available for more than eight of these years. If one thinks of the x-ray picture eight years after that discovery and compares it with that of today, one may be encouraged to be very optimistic about isotopes.

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# IDIOPATHIC CARDIAC HYPERTROPHY*

## Report of 3 Cases

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IN most cases of cardiac hypertrophy an antecedent cause, such as hypertension, valvular disease or coronary arteriosclerosis, is easily demonstrable. Hypertrophy in certain patients with congestive heart failure exists without evidence of any of the known causes of heart disease.

The first recorded case of so-called idiopathic hypertrophy of the heart was described in 1901 by Josserand and Gallavardin.[1] In 1944 Levy and Von Glahn[2] collected 14 cases from the literature and added 10 of their own. Other contributors[3-16] have brought the total number of cases in the literature to 46. Three more cases are presented below.

### CASE REPORTS

CASE 1. W.K., a 43-year-old man, was well until April, 1946, when anginal symptoms 1st occurred and were followed by cardiac decompensation. He was hospitalized in November after a period of outpatient treatment for cardiac failure.

The blood pressure was 122/70. The heart was not enlarged, but the presence of atrial fibrillation was noted. The lungs were clear, and there was no evidence of right-sided heart failure. Stigmas of arteriosclerosis and hyperthyroidism were not present. Blood counts were normal, and urinalysis and serologic tests for syphilis were negative. An x-ray film of the chest showed borderline enlargement of the heart and an increase in the pulmonary vascular markings. The presence of atrial fibrillation was confirmed by an electrocardiogram. Multiple premature ventricular contractions and nonspecific T-wave changes were also evident in the tracing.

After digitalization, with good response, the patient was discharged from the hospital to continue maintenance digitalis. Within 6 weeks failure recurred, and he was readmitted to the hospital on April 15, 1947. The heart was clinically enlarged, and atrial fibrillation was still noted. The lungs were congested, the liver enlarged, and the ankles swollen. X-ray films of the chest demonstrated a small amount of pleural effusion on the right. Laboratory studies were again within normal limits.

Compensation was quickly re-established on bed rest, low-salt diet, ammonium chloride and continued digitalization. He was discharged from the hospital in 3 weeks with a recommendation to continue the digitalis and low-salt diet.

For 19 months symptoms were minimized with Mercuhydrin injections twice weekly; then recurring episodes of failure resulted in a 4th hospital admission on December 26, 1951, when the heart was greatly enlarged and atrial fibrillation was present. The basal metabolic rate was +4 per cent. Routine laboratory studies were normal. An unsuccessful attempt to convert the atrial fibrillation was made after preliminary treatment with anticoagulants. The patient was discharged, improved, in 5 days.

The temperature was normal. The pulse was 112 and irregular, and the blood pressure 134/88.

Failure returned and progressed, and the patient was admitted for the last time on March 1, 1952. The heart rate was 100, and the rhythm irregular. The blood pressure was not obtainable. The heart was enlarged to both right and left. The abdomen was distended, and the liver edge was palpated 3 cm. below the right costal margin. Pitting edema of the lower extremities was present, and shortly after admission a bloody diarrhea occurred. Within a few hours the patient died.

At autopsy the heart weighed 800 gm. All chambers were dilated to at least twice the normal size. There was a mild degree of thickening of the mitral valve. The wall of the right ventricle was 5 mm., and that of the left 15 mm. thick. The myocardium was pale-reddish color with a limited degree of grayish streaking. At the apex of the left ventricle a 1.5-cm. area of subendocardial scarring was present. There were no mural thrombi. The coronary arteries were normal.

The lungs were markedly congested. All visceral organs showed passive congestion. The thyroid and adrenal glands were normal. Microscopical examination of the heart revealed hypertrophy of the myocardium, with vacuolar degeneration and passive congestion.

The presence of angina, cardiomegaly, atrial fibrillation and heart failure in this case led to a diagnosis of arteriosclerotic heart disease. Autopsy disclosed no cause for the cardiac hypertrophy.

CASE 2. W.N., a 38-year-old man, was 1st hospitalized in August, 1950, with a 7-year history of peptic ulcer. An acute bout of alcoholism followed by hematemesis resulted in the 1st hospitalization. For a week before discharge on September 22 tachycardia (rate of 100-120 beats per minute) was recorded but not evaluated.

For a 3-month period the patient was asymptomatic, but then had epigastric distress for 1 year. Again, alcoholism and hematemesis resulted in hospitalization. The temperature was normal; the pulse was 132 and regular, and the blood pressure 105/90. He appeared in no distress, and auscultation of the heart revealed no abnormality except tachycardia. Laboratory studies were normal. The basal metabolic rate was −7 per cent. An electrocardiogram demonstrated sinus tachycardia and low-voltage QRS complexes. The pulse rate of 90 to 100 beats per minute persisted until the week before discharge. The level of protein-bound iodine in blood drawn during this hospitalization was later reported as 6 microgm. per 100 cc., with a soluble fraction of 3.9 microgm. per 100 cc. The patient was discharged on February 14, 1952.

In May occasional sticking precordial pain progressed to severe persistent pain, accompanied by dyspnea, orthopnea and ankle edema. He was readmitted to the hospital on May 9. A mild tachypnea and tachycardia (rate of 110), with a blood pressure of 80/60, were present. Rales were heard in the right-lower-lung field. The heart was now slightly enlarged, and the heart tones were distant. Hemogram and urinalysis were again normal. Serologic tests for syphilis, blood urea nitrogen and electrolytes were within normal limits. X-ray examination showed generalized cardiac enlargement and pulmonary congestion. Three days later the lungs were clear, but the enlargement persisted. The venous pressure was equivalent to 120 mm. of saline solution, and the circulation time (arm to tongue, with Decholin) was 32 seconds. The patient was digitalized, placed at bed rest and given a low-salt diet. By July 1 the heart was of normal size. Electrocardiograms recorded a persistent sinus tachycardia, with general low voltage and T-wave inversion in Lead aVL. Tachycardia continued, the rate varying between 110 and 160 beats per minute. Increased dosages of digitoxin did not modify the tachycardia. He left the hospital on July 23, less dyspneic but still orthopneic.

In November a 4th hospital admission resulted from a leg fracture sustained in an automobile accident. Tachycardia was still present, with no change in the physical findings, electrocardiograms or roentgenograms. Serial electrocardio-

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grams over a 3-month period disclosed sinus tachycardia and nonspecific T-wave changes. For a 60-day period propylthiouracil was administered empirically for tachycardia, without beneficial effect. The patient was also empirically given multivitamins. He again improved subjectively and was discharged in March, 1953.

Cardiac failure recurred, and he was readmitted to the hospital on May 25. The pulse rate was 138, and the blood pressure 78/52. The border of the heart extended to the left anterior axillary line. The liver was enlarged, and considerable ankle edema was present. Electrocardiograms were unchanged from those of previous admissions.

Again, he responded to routine cardiac measures and was discharged, only to be readmitted in 3 weeks with recurrence of congestive heart failure. The pulse rate was 140 per minute, and the rhythm was regular. The blood pressure was 108/60. Increased cardiomegaly and bilateral hydrothorax were seen on x-ray study. Subsequently, a pulmonary infarction in the right lung occurred. The electrocardiogram was unchanged. After further pulmonary infarctions the patient failed progressively. He died on November 8.

At autopsy the heart weighed 600 gm. The coronary arteries were patent and smooth, with no evidence of atherosclerosis. The wall of the left ventricle at the outflow tract measured 15 to 18 mm., and that of the right ventricle 4 to 8 mm. The valves were normal. At the apex of the heart mural thrombi were firmly attached.

Multiple emboli were present in the lungs with pulmonary infarctions. The abdominal viscera showed typical changes of chronic passive congestion. The adrenal and thyroid glands were normal.

The myocardial fibers were moderately hypertrophied, and scattered small zones of replacement fibrosis were seen. Organizing mural thrombi were observed in both ventricles. Interstitial edema of the myocardium was also noted.

During life, diagnoses ranged from an early impression of tachycardia on the basis of anxiety to beriberi or thyrotoxicosis. No satisfactory explanation for the tachycardia could be confirmed by diagnostic methods. Because of lack of evidence for other causes of heart failure and with the history of an episode resembling angina, this case was labeled arteriosclerotic heart disease. Once more autopsy failed to reveal a reason for the cardiac hypertrophy.

Case 3. C.H.B., a 28-year-old man, in December, 1944, because of substernal pain regarded as representing an acute myocardial infarction, was transferred to the Brown General Hospital after 2 months' treatment with bed rest. The past history was noncontributory. On admission the patient was found to be in no distress. The blood pressure was 120/80. Physical examination was within normal limits. A complete blood count was normal, and urinalysis and serologic tests for syphilis were negative. Roentgenograms in December showed marked cardiac hypertrophy but clear lung fields. X-ray study on February 9, 1945, demonstrated only slight cardiac enlargement. On December 12 electrocardiograms revealed inverted T waves in Lead 1 and diphasic T waves in Lead 2. Eleven days later the T waves were inverted in Leads 1, 2 and $CF_4$. On this admission the T waves were flat or small. An occasional extrasystole was present. The patient was discharged on no medication, after an uneventful hospital stay, with a diagnosis of myocardial infarction. In retrospect, evidence was insufficient for such a conclusion.

In August, 1950, an appendectomy was performed. The heart and lungs were normal, although a history of transient episodes of shortness of breath, orthopnea and ankle edema was obtained. The patient had been digitalized by his private physician. X-ray examination showed the heart to be of normal size, and the electrocardiogram was unchanged from previous tracings.

In October, 1952, it became impossible for him to conduct his business as a photographer owing to progressive cardiac decompensation. He was admitted to the hospital on December 16, 1953, with a 2-week history of cough and hemoptysis. A transient paralysis of the left arm and an aphasia of 1 day's duration, occurring 1 month before admission, were described.

The patient appeared chronically ill and was producing bloody sputum. The temperature was normal. The pulse rate was 104, and the blood pressure was 98/60. Rales were present in the left lateral portion of the chest. The heart extended to the left anterior axillary line, and atrial fibrillation was present. The liver was enlarged. There were marked varicosities of the legs, and + pitting edema was evident. Laboratory studies were normal. A subsequent leukocytosis (white-cell count of 15,700 with 80 per cent neutrophils) developed. X-ray examination of the chest showed pulmonary infarction in the right-lower-lung field, and the heart was enlarged. One week later bilateral pulmonary infiltrations were noted.

Hemoptysis persisted and pleuritic pain in the left side of the chest developed. Treatment consisted of codeine, digitalis, aminophylline and penicillin. The patient continued to fail and died on December 24.

At autopsy the heart weighed 700 gm. and was tremendously dilated. All the valves were normal. The papillary muscles were extremely thick, being 2 or 3 times the normal size. In the left ventricle was an almond-sized thrombus. The apex of the right ventricle contained a plum-sized thrombus. There was no evidence of myocardial infarction, and the coronary vessels were patent and smooth.

The lungs contained numerous fresh thrombi and many areas of pulmonary infarction. The viscera were congested.

Microscopical examination of the coronary vessels was negative. The muscle fibers of the right ventricle contained many vacuoles. The interventricular septum and the left ventricle were distinctly hypertrophied, with vacuolar degeneration of some fibers. Mural thrombi were present in both ventricles.

The lungs showed congestion and infarction. There was some depletion of adrenocortical lipids, but the organs were otherwise normal. The thyroid gland contained a few small zones of lymphocytic infiltration but was otherwise normal.

This is the second case in this series with mural thrombi of the ventricles. Such thrombi were noted in about a third of the reported cases of idiopathic hypertrophy. The changes are not limited to this disorder but may be seen in other conditions causing cardiac hypertrophy.[17]

## Discussion

Hypertrophy of normal hearts, if it occurs at all, is unusual as evidenced by studies of athletes undergoing extreme exertion.[18] The relation of arrhythmia and hypertrophy in normal hearts has not been found to be one of cause and effect.[19-22]

Although few cases have been reported to date and no statistical evaluation can be made, a characteristic pattern is evidenced by these cases. All patients had cardiac hypertrophy, demonstrable by physical examination, x-ray study and electrocardiogram. Congestive heart failure was present in all but 1 case. Tachycardia and arrhythmias were the rule. A small number of patients showed the phenomenon of peripheral embolization, and in an occasional case this was the striking feature. Angina was occasionally present, as was fever. In almost every case antecedent hypertension was absent, and the few cases in which it was present should perhaps not be considered in this category. Significant murmurs were universally absent. Nutritional data were not given, but in the cases reported above only 1 patient had a grossly deficient food intake. However, he did not improve on

thiamine and his circulation time was prolonged.

Survival after the first symptoms differed widely, varying between several days and six years. Age of onset varied from youth to old age, and similar conditions have been described in children. Most of the cases were in males, and most in members of the white race.

At autopsy hypertrophy was always present, and dilatation was frequent. Myocardial degeneration and fibrosis was minimal when present. In about half the cases there was subendocardial fibrosis with or without mural thrombi. A recent paper by Thomas and his associates[23] discusses many of the same cases of cardiac hypertrophy and emphasizes the endocardial fibroelastosis as perhaps an etiologic factor.

The mechanism for cardiac hypertrophy is not well understood. Most authors consider it to be secondary to dilatation. Little is known about the fundamental biologic processes that produce hypertrophy of the heart. In most cases associated with congestive heart failure the underlying etiologic condition is easily recognized clinically or pathologically by well established criteria for diagnosis. However, a certain number of cases of congestive heart failure associated with hypertrophy do not lend themselves to such a classification. Several classifications have been proposed, all of which acknowledge unexplained hypertrophy.[24-26]

Wiggers[27] tried to find a common denominator in cases of hypertrophy and subscribed to Horvath's theory of hypertrophy from mechanical effect—that is, increased stretch on the myocardium due to increased ventricular filling because of valvular defects or resistance to outflow. This was verified by Eyster et al.[28] in experiments on dogs.

In 1951 Simkins[12] presented a case similar to those under discussion and suggested possible mechanisms for hypertrophy. One of these mechanisms was vitamin B deficiency. The present cases clinically do not fit the criteria of beriberi heart disease.

Exercise has been considered a cause for cardiac hypertrophy,[8,15] as has previous hypertension. The patients described above gave no history of undue exertion and were selected on the basis of the absence of known hypertension during protracted periods of observation.

Arrhythmias have also been considered a cause of cardiac failure and hypertrophy.[29-32] Several authors,[21,30,33,34] however, have stressed the benignity, reversibility and generally good prognosis in the arrhythmias occurring in otherwise normal hearts.

Anoxia has been proposed as a basic abnormality in cardiac hypertrophy (Lewis), but the suggestion has been refuted by a series of experiments in which isolated heart muscle perfused under anoxic conditions for relatively short periods showed no hypertrophy.[35] We believe that these results do not obtain in human beings to whom relative anoxia would be applied for long periods.

It has also been pointed out that aviators and others exposed to hypoxic conditions had no cardiac hypertrophy.[27] However, this also may not be analogous to prolonged hypoxia over a matter of years. In mountain dwellers other compensatory mechanisms exist, and anoxia is not actually present at the tissue level.

Evidence of hypoxia as a factor in cardiac failure is contributed by Miller et al.,[36] who, in a study of the arterial oxygen saturation in emphysematous patients, found congestive cardiac failure limited almost entirely to patients with transient or persistent hypoxemia. Harvey and his co-workers[37] were able to demonstrate that failure due to cor pulmonale could be prevented if arterial oxygen saturation was maintained within normal limits.

The differential diagnosis of idiopathic cardiac hypertrophy most often lies with arteriosclerotic heart disease. However, the criteria for diagnosis of arteriosclerotic heart disease were usually absent.[28] Some of the cases, especially those with angina, could not be differentiated. Other conditions considered in differential diagnosis are beriberi heart disease, thyrotoxic heart disease, myocarditis, subendocardial fibrosis, Von Gierke's disease and amyloid disease of the heart.

Electrocardiographic evidence of myocardial infarction has not been demonstrated in any of the reported cases of idiopathic cardiac hypertrophy. One might then assume that these specific electrocardiographic changes would rule out this condition, but it has been recognized that infarction patterns may follow paroxysms of tachycardia[38,39] or emboli of coronary vessels.

Angina without other adequate explanation is usually considered presumptive evidence of arteriosclerotic heart disease. However, pulmonary hypertension, nonarteriosclerotic myocardial ischemia and even noncardiac causes can give anginalike symptoms. Angina is an exceedingly difficult complaint to evaluate.[40]

T-wave and ST-segment changes are prevalent in many cardiac disorders and cannot be regarded as conclusive evidence of arteriosclerotic heart disease.[41,42] Youth does not exclude diagnosis of arteriosclerotic heart disease. It can be demonstrated that cardiomegaly occurs in arteriosclerotic heart disease without failure.[43,44] This finding of hypertrophy is of no specific diagnostic value by itself.

In many cases differential diagnosis is difficult. However, when congestive heart failure and cardiomegaly exist without angina or the pattern of infarction seen on the electrocardiogram or other demonstrable cause of failure, the presumptive diagnosis of idiopathic cardiac hypertrophy may be made.

## Summary

Three cases of idiopathic cardiac hypertrophy are reported, bringing to a total of 49 the number of such cases in the literature.

Some of the views on the stimulus to myocardial hypertrophy are reiterated.

The clinical characteristics are briefly outlined.

The difficulties of differential diagnosis of idiopathic cardiac hypertrophy from arteriosclerotic heart disease and other types of heart disease are discussed.

We are indebted to Drs. J. Harold Kotte and Arnold Iglauer, of the Cincinnati General Hospital, Cincinnati, Ohio, for their critical reading of the manuscript.

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# OBSERVATIONS ON THE ANTIBODY CONTENT OF THE BLOOD IN PATIENTS WITH MULTIPLE MYELOMA*

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GREAT advances have been made in knowledge and understanding of the complex factors concerned in resistance or susceptibility to infection, but much remains that is controversial or incompletely understood.

The current widespread interest in and demonstrated value of gamma-globulin administration in the prophylaxis of certain infectious diseases, such as viral hepatitis, has served to call attention to this constituent of the plasma proteins and its role in protection against infection. The recognition in recent years of that rare disorder, agammaglobulinemia, and the greatly increased susceptibility to infections in such patients, has also stimulated interest in gamma globulin and its ability to protect against infection. It is generally agreed that most circulating antibodies are found in the gamma-globulin fraction of the plasma proteins although it seems clear that gamma globulin and antibodies are not synonymous terms. Dysproteinemia, with striking increases in gamma globulin, is a common finding in many cases of myelomatosis. Nevertheless, one may encounter an occasional patient suffering from multiple myeloma who manifests a striking susceptibility to pneumonia, and

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frequent recurrences of acute, often severe, pulmonary infection may be a striking feature of the clinical course in such a patient. This tendency may be observed when he is not otherwise incapacitated and may be the first symptom that leads him to seek medical advice. One of the patients in the present study was first seen because of the third attack of acute lobar pneumonia occurring in a period of four months; he continued to suffer from repeated attacks between his first admission to the hospital in March, 1951, and the time of his death in June, 1953. Another patient (Case 7) was admitted to a hospital because of pneumonia in 1950, when the diagnosis of multiple myeloma was first made. Between that time and April, 1954, he had ten attacks of acute pneumonia.

In 1945 Bee,[1] reporting 10 cases of myelomatosis, described multiple pneumonic episodes in 2 patients. He expressed the opinion that gradual deformity of the chest was a predisposing factor in the repeated attacks of pneumonia, but also suggested that changes in serum globulins might be responsible for altered immunity and increased susceptibility. No structural abnormalities of the thorax or its contents, such as bronchial obstruction, were present in our patient, who was well nourished and muscular when first seen. An immunologic study was undertaken to determine whether there was a general deficiency of antibodies, which might indicate an inability to form protective antibodies, and studies are under way to ascertain whether patients with myelomatosis are able to form specific antibodies in response to the administration of various antigens.

## Methods and Materials

The diagnosis of multiple myeloma was established in each patient by biopsy of the bone marrow or by autopsy or both.

The antibodies studied were agglutinins for *Salmonella typhosa* (901), *Paracolobactrum ballerup* (481), opaque forms,* *Escherichia coli* (3564), opaque form,* sheep erythrocytes and type-specific agglutinins for human A and B erythrocytes, lysins for *S. typhosa* (901) and *Esch. coli* (3564), opaque form, and sheep cell (amboceptor).

The presence and titer of complement were also determined in all cases. The specified antibodies and complement were selected for this investigation only because their presence and titer in control subjects were available from other work done in this hospital and at Brown University, or in the immunologic literature.

Dilutions in saline solution from 1:5 or 1:10 to 1:1280 were made from the inactivated serums of patients and controls. Agglutinins for the somatic and flagellar fractions of *S. typhosa* were obtained with living cultures of O-901 and H-901 respectively. The alpha agglutinins were determined with a viable culture (3564 opaque) rich in alpha antigen. All tests employing bacterial antigens were read after four hours' incubation at 37°C. and again after eighteen hours' incubation at 55°C.

To ascertain titers for sheep cells impregnated with saline extract of *P. ballerup* (481 op antigen) inactivated serums were adsorbed with washed sheep cells to remove all normal sheep-cell antibodies. The adsorbed serums were tested in serial dilutions previously specified with sheep cells impregnated with 481 op antigen. All agglutination tests using blood cells as antigen were recorded after four hours at 37°C. and again after eighteen hours at 20°C. The presence and titer of sheep-cell agglutinins and the titer of human type-specific alpha and beta agglutinins were determined in the conventional manner. (Sheep-cell agglutinin titers in this work were higher than those normally encountered because a much lighter suspension of sheep cells was used than is employed in the test for heterophil antibodies in the diagnosis of infectious mononucleosis.[2,3])

Dilutions of inactivated serums, washed sheep cells and guinea-pig complement were employed to show the presence and titer of normal sheep amboceptor. Complement titers were obtained by addition of sheep cells sensitized with immune sheep-cell amboceptor to dilutions of fresh serums from patients or controls. The tests for normal sheep-cell amboceptor and complement were read after thirty minutes in a 37°C.-water bath.

With one exception all patients with multiple myeloma were World War I veterans or of a comparable age group. In the selection of controls it was recognized that the age group involved could play an important part in the presence and titer of antibodies against *S. typhosa*. Accordingly, all control serums for the O and H antibodies of *S. typhosa* and the 481 op antigen were taken from World War I veterans. When other antibodies were concerned both World War I and II veterans were used. Except for work on human type-specific agglutinins control serums were selected as described above from patients admitted to the medical and surgical wards of the hospital for diseases other than multiple myeloma and from normal persons.

The serums of 4 patients with multiple myeloma were compared with control serums for their effect on the phagocytic action of polymorphonuclear cells against *Micrococcus pyogenes* var. *aureus*. The serum of 3 patients with multiple myeloma, including Case 1, showed weak phagocytic action compared with

*The opaque form of *P. ballerup* (481) contains an antigen (op antigen) that makes this form completely or almost completely inagglutinable in antiserum with high concentrations of specific antibody. When heavy suspensions of the opaque form are boiled in saline solution for one hour and centrifuged at high speed the op antigen is found concentrated in the supernatant fluid. Sheep cells, which readily absorb the op antigen from such fluids, are agglutinable and are used in hemagglutinin tests to detect the op antibody in serums. In England considerable difficulty has been encountered in diagnostic work with enteric bacteria because of a common antigen (alpha) in salmonella, paracolobactrum and escherichia and alpha antibodies in normal and immune serums. The alpha antigen is essentially an opaque antigen. Nevertheless, some cultures with the alpha antigen show no inagglutinability whereas others exhibit varying degrees of inagglutinability. An agglutinable culture of *Esch. coli* (3564), opaque form rich in alpha antigen, was used in the present work.

that of the controls whereas the serum of Case 2 failed completely to promote phagocytosis. The control serums demonstrated normal phagocytic action.

## Results

Table 1 shows the occurrence and average titer of antibodies and complement in control groups.

Table 2 summarizes the findings in 9 patients with myelomatosis. Four patients showed no antibodies, including the blood-group antibodies, 2 on the initial examination and 2 on subsequent examinations. It was possible to make only a single examination in the other 5 cases. Although some antibodies were present in the serum of these 5 patients, only Case 3 showed what may be considered a normal content of these substances. Case 4 is considered to have had a deficiency of antibodies; isoagglutinins were present in unusually low titer, and amboceptor was absent. Cases 5, 6 and 8 were definitely abnormal in that isoagglutinins were either deficient or absent in all 3 and very few other antibodies were found. Not every normal person or control patient has every one of the antibodies included in this investigation, but the complete absence of all antibodies or lack of the appropriate isohemagglutinins was not observed in this study except in patients with myelomatosis. There is reason to believe that further tests in the 5 patients in whom only a single examination was made would show progressive decrease and ultimately complete or nearly complete disappearance of circulating antibodies. Amboceptor was not detectable at any time in the serum of the 9 patients with multiple myeloma, although it was present in 97 per cent of controls. None of these nine patients showed agglutinins for a deficiency of antibodies in December, 1952. Subsequent examinations in April and May, 1953, showed a decrease in the few antibodies present and their final complete disappearance. In May, 1953, complement, which had previously been present in normal titers, was also absent. All the other 8 patients with myeloma had complement in normal titers even when all antibodies had disappeared.

Table 1. *Occurrence and Average Titer of Antibodies and Complement in Control Groups.*

| Antibody | No. of Serums | Percentage Positive | Average Titer |
|---|---|---|---|
| Agglutinins for: | | | |
| O-901 | 188 | 84 | 1:35 |
| H-901 | 188 | 84 | 1:60 |
| 3564 Op | 168 | 56 | 1:135 |
| NSC | 156 | 95 | 1:70 |
| 481 Op | 124 | 77 | 1:65 |
| A cells | 100 | 100 | 1:95 |
| B cells | 113 | 100 | 1:40 |
| Lysins for: | | | |
| O-901 | 39 | 67 | 1:80 |
| H-901 | 37 | 79 | 1:35 |
| 3564 Op | 51 | 92 | 1:65 |
| Amboceptor | 100 | 97 | 1:390 |
| Complement | 100 | 100 | 1:90 |

Figure 2 shows the findings in Case 2, in which antibodies except amboceptor were present in a normal titer in January, 1953, but all antibodies were absent ten months later. How soon after the first examination these antibodies disappeared is not known

Table 2. *Titers of Antibodies in 9 Patients with Myelomatosis.*

| Case No. | Blood Group | Agglutinin for O-901 | Agglutinin for H-901 | Agglutinin for 3564 OP | Agglutinin for NSC | Agglutinin for 481 OP | Agglutinin for A Cells | Agglutinin for B Cells | Lysin for O-901 | Lysin for H-901 | Lysin for 3564 OP | Amboceptor | Complement |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *titer* | *titer* | *titer* | *titer* | *titer* | *titer* | *titer* | *titer* | *titer* | *titer* | *titer* | *titer* |
| 1 | A | — | — | — | — | — | — | — | — | — | — | — | — |
| 2 | A | — | — | — | — | — | — | — | — | — | — | — | 40 |
| 3 | O | — | — | — | 1:10 | — | 1:160 | 1:80 | 1:5 | 1:5 | 1:160 | — | 320 |
| 4 | O | — | — | 1:10 | — | — | 1:5 | 1:10 | — | — | 1:40 | — | 160 |
| 5 | O | — | — | 1:10 | — | — | — | 1:20 | — | — | 1:80 | — | 160 |
| 6 | O | — | — | — | 1:20 | 1:40 | — | — | 1:10 | 1:5 | 1:40 | — | 160 |
| 7 | B | — | — | — | — | — | — | — | — | — | — | — | 160 |
| 8 | A | — | — | — | — | — | — | — | — | 1:40 | 1:20 | — | 40 |
| 9 | O | — | — | — | — | — | — | — | — | — | — | — | 80 |
| Controls | — | 1:35 | 1:60 | 1:135 | 1:70 | 1:65 | 1:90 | 1:40 | 1:80 | 1:35 | 1:65 | 1:390 | 90 |

Salmonella O and H-901, although these antibodies were found in 84 per cent of control subjects.

As indicated above, repeated testing has demonstrated a decrease in the number and titer of antibodies and, in 2 patients, complete disappearance. Figure 1 presents the findings in Case 1. There was since there was an unavoidable lapse of ten months before the second test was made.

Analysis of serum proteins by filter-paper electrophoresis was done in 5 patients (Cases 1, 2, 7, 8 and 9), all of whom demonstrated deficiency of antibodies, which in 4 of the 5 patients were absent. Four

showed a high peak of gamma globulin, and the fifth a tall peak representing the so-called M component (Fig. 3*A*).

Case 9, who showed the peak M component, was of added interest because electrophoretic analysis revealed absence of gamma globulin. He was nevertheless remarkably free from infection, in contrast to the patients with agammaglobulinemia described in medical reports and especially to a patient (Case 1), who had a pronounced increase in gamma globulin

FIGURE 1. *Antibody Titers in Case 1 in December, 1952, and in April and May, 1953.*

*The numerals at the top (and also those at the top in Figure 2) indicate the titer of antibodies as determined by serial dilutions ranging from 1:10 to 1:320. The symbols at the left indicate the antibodies studied; those above the horizontal line were measured in serum inactivated by heating to 55°C., and include agglutinins and amboceptor, and those below the line were measured in noninactivated serum and include lysins for three organisms. The titer of complement was also determined. O-901 and H-901 refer to standard typhoid organisms; 4 OP indicates* Esch. coli *(3564), opaque form; A and B indicate isoagglutinins for human A and B cells; NSC refers to agglutinins for normal sheep erythrocytes, and 481 to sheep cells impregnated with saline extract of* P. ballerup. *AMBO indicates amboceptor, and COMP complement.*

and suffered from frequently recurring episodes of pneumonia over a period of two and a half years (Fig. 3*B*). Both patients showed absence of antibodies.

## Discussion

No significant difference between 2 patients with multiple myeloma suffering from recurring pneumonia and other patients with myelomatosis was demonstrated so far as the presence and titer of circulating antibodies, electrophoretic patterns and the concentrations of serum globulin and gamma globulin were concerned. The results of this study provide no explanation, therefore, for the clinical phenomenon observed in a few patients with myeloma who have an extraordinary tendency to repeated attacks of pneumonia. Nevertheless, deficiency of circulating antibodies appears to be a consistent and characteristic feature of myelomatosis. We know of no disease except agammaglobulinemia in which a comparable deficiency of antibodies occurs. It is believed that this abnormality, combined with the progressive decrease and ultimate disappearance of all antibodies, including the isoagglutinins, which has been observed in patients with myelomatosis, may be of diagnostic aid in rare cases in which the usual clinical and laboratory findings may be absent or equivocal. Observation of a larger number of cases will be necessary before one can say whether or not this opinion is sound.

The ability of patients with myeloma to produce specific antibodies in response to stimulation by injection of antigens has not been adequately studied. Pneumococcus capsular polysaccharide was given to 1 patient, who showed no production of antibodies. The results of this single observation were inconclusive. Moreover, even normal persons may demonstrate little or no antibody production in response to such a procedure. Further studies of this feature of the disease are being carried out. Larson and Tomlinson,[4] in investigating the relation between alterations in serum protein concentrations and antibody production, included 4 patients with multiple myeloma in the group of 12 cases studied by them. Measurement of the amount of precipitable antibody nitrogen formed in response to the administration of type-specific pneumococcus capsular polysaccharide 1 and

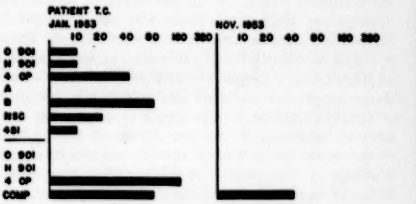



FIGURE 2. *Antibody Titers in Case 2 in January and November, 1953.*

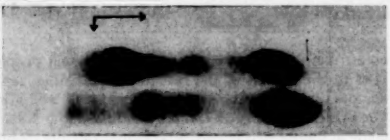
*Numerals and symbols at the top and side are explained in the legend of Figure 1.*

2 in the 4 patients with myeloma indicated little or no antibody production. Balch,[5] studying the role of nutritional deficiency in antibody formation, observed a normal production of diphtheria antitoxin in one patient with myelomatosis.

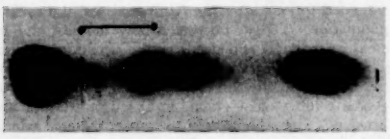
Gamma globulin as found in normal human serum is a heterogeneous protein, and subgroups have already been identified.[6] The gamma globulin that is so strikingly increased in many patients with myelomatosis probably differs significantly from normal gamma globulin and from that found in patients with other diseases, in whom there is an increase in gamma globulin. Conn and Klatskin[7] stressed the shape of the gamma-globulin peak and the peak of other globulins, which may be increased in multiple myeloma. They point out that the peaks are characteristically tall and narrow, indicating a relatively homogeneous protein. Present information suggests that plasma cells are primarily responsible for antibody formation[8-12] and that circulating antibodies are found in

the gamma-globulin fraction of plasma proteins. It seems paradoxical, therefore, that there should be a deficiency or absence of antibodies in a disease such as myelomatosis in which there is marked proliferation of plasma cells, hyperglobulinemia and frequently hypergammaglobulinemia. This seeming paradox may be due to the fact that the plasma cells in multiple myeloma, being malignant, are therefore abnormal cells that synthesize abnormal proteins of various types at the expense of normal proteins, including antibody proteins. Such an explanation is consistent with the opinion that the gamma globulin in myeloma is abnormal and significantly different from that found in normal human serum.

Balch's[5] demonstration of normal antibody production in spite of extensive body wasting indicates that malnutrition was not the cause of the deficiency in our patients. Moreover, 1 patient (Case 1), who showed absence of all antibodies, was well nourished, muscular and vigorous when this abnormality was first noted. Other causes such as distribution and rate of destruction of antibodies must be considered as possible explanations for the deficiency of circulating antibodies observed in this study. Experience with Case 1, in which transfused antibodies disappeared in a few hours from the patient's blood, indicates that such factors may be responsible. The observation of Kass,[13] who noted abnormally rapid catabolism of tagged gamma globulin administered to a patient with multiple myeloma, emphasizes the possible importance of increased rate of destruction as a reason for the deficiency of circulating antibodies.



A



B

FIGURE 3. *Electrophoretograms of Serum Proteins Using Filter-Paper Technic with Barbiturate Buffer at pH 8.6, Ionic Strength 0.05 (the Vertical Arrow Indicates the Point of Origin, and the Horizontal Arrow the Direction of Migration toward the Positive Pole).*

A=*Case 9 (upper) and normal control (lower). The dense concentration just to the right of the point of origin in the patient's electrophoretogram shows the large amount of M component present in this patient's serum; little or no gamma globulin is present.*

B=*Case 1. The great increase in gamma globulin is shown by the dense concentration to the left of the point of origin.*

## SUMMARY AND CONCLUSIONS

A study of the occurrence and titer of certain antibodies in 9 cases of multiple myeloma in comparison with those in normal persons and patients with diseases other than myeloma was carried out.

Complete absence of antibodies or a marked deficiency of these substances is a characteristic feature of myelomatosis. In an occasional patient a definite abnormality may not be found on the initial examination, but repeated testing will show progressive decrease and ultimately complete or nearly complete disappearance of antibodies.

Analysis of the serum protein by filter-paper electrophoresis was done in 5 patients. Four showed marked increase in gamma globulin, and the fifth a tall peak of the so-called M component but no gamma globulin. Four of these patients demonstrated complete absence of antibodies, including the isoagglutinins, and the fifth almost complete absence of antibodies. The latter patient also had no isoagglutinins.

The immunologic abnormality demonstrated in multiple myeloma is considered to be the result of abnormal function of the malignant plasma cells whereby deranged protein synthesis results in the production of abnormal proteins at the expense of normal proteins, including antibody protein.

Since this paper was submitted for publication our attention has been called to the observations of Marks,[14] who determined the circulatory levels of staphylococcal α-antitoxin and antistreptolysin O in 17 patients with myelomatosis in comparison with levels found in normal persons and patients with hyperglobulinemia due to disorders other than myelomatosis. Eight of 17 patients with myelomatosis showed markedly low levels of one or both antitoxins, and 5 others moderately low values. Among cases with hyperglobulinemia from other causes levels of antitoxin were normal or increased. Marks concluded that myelomatosis is "frequently associated with depressed antibody formation," an effect that he attributed to the deranged growth of plasma cells. He suggested that serologic studies might be useful in the diagnosis of myelomatosis with hyperglobulinemia. However, Case 5 in our study showed a deficiency of antibodies, including isoagglutinins, although at that time he did not have hyperglobulinemia, the serum globulin being 2.2 gm. per 100 cc.

We are indebted to Drs. M. N. Fulton, J. M. Beardsley and Gustavo A. Motta, of Providence, Rhode Island, to Dr. S. D. Clark, of Bristol, Rhode Island, and to Dr. Chauncey Stone, of the Veterans Administration Hospital, Coral Gables, Florida, for giving us the opportunity to make observations and antibody studies on several patients included in this report.

Antibody determinations were done by Helen Seraichekas, B.S., and Dorothy Oborne, A.B., and electrophoresis of serum proteins by Miss Oborne.

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## SPECIAL ARTICLE

# PROBLEMS OF MEDICAL PRACTICE IN INDIA

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SIXTY thousand doctors, for a population of 360,000,000 people in India, is the usual reply given to the usual question asked by foreign colleagues and friends. But unless further amplification is demanded or given, the reply is only partially true.

To understand the present problems of medical practice in India, it is necessary to have some information about the background of Indian conditions.

### Historical Background

India is an ancient country, with traditions and knowledge dating from thousands of years ago. The people of India, of the earliest days, developed among other things a medical science known as Ayurveda — the science of life — long before any such science appeared to be known anywhere else in the world. This science was based on the three principles of observation, experimentation and deductions, and with a philosophy of its own. For medicine Ayurveda used preparations from herbs, plants, minerals and other sources. There was Ayurvedic anatomy and surgery. It reached its peak of performance and then gradually stagnated and decayed. Why this happened is not known. The art and science of Ayurveda were handed down, according to the principle of preceptorship, from teacher to pupil.

With the invasion of Islam into India, Ayurveda received a setback, and Arabic medicine was introduced into the country; it is known as "Unani."

These two systems held the field side by side during the Muslim rule in India, the knowledge and education being imparted to new entrants into the profession according to the preceptorship principle. Dissection of human bodies for purposes of learning anatomy became taboo, and the teaching gradually more and more empirical. Practice of medicine was confined to drug therapy only.

Apart from these two systems, there were the usual home remedies, handed down from grandmothers to mothers and daughters. There were also charms and cures, "revealed" to various pious and chosen people.

With the advent of the British rule in India, some doctors came from the United Kingdom to look after the British residents of India. Gradually, the Indian medical service was begun, with British doctors mainly to look after the British personnel. This was gradually extended to look after the Army and also the civilian population. To get doctors locally to meet the increasing demand and needs of the situation, medical schools and colleges were gradually started in various parts of India, the three oldest colleges — which are over a century old — being in Calcutta, Madras and Bombay. The schools used to impart medical education of a lower standard to students with lower basic education; the colleges imparted education of a higher (and university) standard to students with higher basic education, the quality being equivalent to that of the British universities and licensing bodies and the Indian degrees being recognized by the General Medical Council in the United Kingdom for purposes of licensing and registration.

Thus, toward the end of the nineteenth century and early in the twentieth, there were various types of people practicing medicine in India: grandmothers, mothers, aunts and daughters using so-called home remedies; quacks, fakirs and Sadhus; Vaids — practicing Ayurveda; Hakims — practicing Unani; licentiates from schools; and graduates of colleges. The last two groups practiced modern medicine. And later a seventh group was added: homeopaths practicing homeopathy.

In the course of time (during the last fifty years) many more colleges were created. Today, practically all the schools of modern medicine have either been closed down or upgraded into colleges. The number of medical colleges — teaching modern medicine — today is about 35, producing between 1700 and 2000 doctors a year.

The situation, however, has been complicated by various factors, as follows:

Two schools are still functioning, producing doc-

*President, Indian Medical Association.

tors of a lower standard than that of graduates from colleges.

In some states, because of the unwillingness of graduates to settle in rural areas, a new type of rural medical practitioner was produced, with lower basic qualifications and lower standards of medical training, on the definite understanding that they would serve in the rural areas for a minimum period of five years. But already they are clamoring for registration on equal terms with graduates, and after five years, most of them are likely to migrate to towns and to compete with fully qualified doctors.

The Vaids and Hakims are either starting their own colleges or persuading the state governments to open new colleges or to subsidize existing ones and to recognize and register the Ayurvedic and Unani diplomas and degrees on equal terms with those of modern medicine.

Another peculiar feature of these new Ayurvedic and Unani institutions is that their students receive some training in modern basic sciences, anatomy, physiology, materia medica, surgery, midwifery and so forth. In some of these institutions the students are taught more of modern medicine and very little of the ancient systems. When they graduate they freely prescribe modern antibiotics and give injections; their training is supposed to be a synthesis of the ancient and modern medicine.

The homeopaths in India, who number over 300,000, are mostly quacks. Few of them are properly qualified physicians who have taken to the practice of homeopathy. There are several hundreds who have qualified from mushroom homeopathic schools and colleges and display diplomas and degrees similar to those of practitioners of modern medicine. The overwhelming majority, who are pure quacks without any training whatsoever, practice medicine with the help of a homeopathic materia medica — and a box of homeopathic medicine.

The homeopaths in India are also clamoring for the establishment of homeopathic colleges by the union and state governments and for license and registration on par with the graduates of modern medical schools. Because of the lack of sufficient qualified doctors of modern medicine, especially in the rural areas, and because of lack of sufficient funds, the union and state governments are in many cases giving in to so-called popular demands, establishing schools and colleges of Ayurvedic, Unani and homeopathic medicine or subsidizing them, either for political reasons or in the hope of creating medical personnel for the rural areas and in some cases of reviving or revitalizing the ancient systems of medicine.

## Medical Practice Today

From the background given above, it should be evident that the practitioners of medicine in India are a heterogeneous group, practicing various types of medicine — from modern scientific medicine down to quackery. There are about 60,000 qualified doctors (including graduates of universities and licentiates from schools) as against a probable 600,000 practitioners of other types. Quackery flourishes in India for various reasons, the main ones being poverty of the people, lack of education, faith in age-old methods and imperfection of the modern system. It must be remembered that modern medicine — in both its diagnostic and its therapeutic aspects — is very expensive and not within easy reach of the poor; it also cannot always cure, and sick people do not easily give up hope, being easily misled by false promises of the quack.

Except in two states in India, there is no restriction on medical practice; anybody, trained or otherwise and qualified or otherwise, can set up in practice openly, and can compete with the best qualified people. Since birth and death certificates are not compulsory in most parts of India, even the indirect restrictions against unqualified practice are not effective.

It is thus apparent that, under the present conditions in India, there is a great deal of inconvenience and hardship to 60,000 properly qualified physicians practicing the modern system of medicine. Out of these 60,000, not more than 15 per cent are in public services employed by governmental hospitals and dispensaries, corporations, municipalities and health services. Besides, the armed forces employ their own medical personnel; in addition railways also have their own medical services. Doctors who are employed in the public-health services are treated as whole-time officers without right of practice and are given salaries and pensions or provident funds or gratuities. Those who are on the medical side are treated as whole-time officers but receive smaller salaries than people in corresponding administrative services and enjoy rights of private practice as well. There is a tendency at present to increase the salaries of the latter officers and to debar them from private practice.

The majority of doctors in this group, however, are in private practice — either as general practitioners or as specialists or consultants. Some of the specialists and consultants hold hospital appointments in an honorary capacity, being paid nothing or almost nothing for services rendered to hospital patients. Because most of the hospitals in the country are owned and maintained by the Government, these hospitals are usually open free of charge to all, poor and rich, and particularly to all Government servants, irrespective of their pay and status. Thus, the honorary staffs have to do a great deal of free work even for the richer section of the community. Most of the doctors, however, are in general practice with their own dispensaries for dispensing medicines to their own patients. Most of the general practitioners give free consultations and advice to their patients in their

surgeries, making a little extra charge for the medicine supplied and for special consultations or injections or home visits and so forth.

It will thus be seen that the general practitioner, to make a decent income, has to work very hard and to see a much larger number of patients than he can do justice to. In some cases chemists' shops either employ or retain the services of qualified doctors to give free consultations to patients, on the basis of salary or commission on the amount realized by the prescriptions.

The social-security scheme or voluntary insurance system is in the stage of infancy, having just been started in a few centers. The health part of this scheme is being covered by whole-time paid officers in three centers. In some other centers the panel system was tried in a modified form, but the payment offered was so meager that the medical associations in these areas rejected the scheme and the Government recruited physicians directly. Recently, somewhat better terms have been agreed upon, and cooperation from the Medical Association has been offered in establishing the panel system. The authorities, however, are in favor of the whole-time service system, and it is not yet certain which system will ultimately prevail.

Hospitals, which are mostly owned and maintained by the Government or corporations or municipalities, are few, the total number of beds being approximately 100,000, including those for tuberculosis and mental diseases.

### Conclusions

The condition of the majority of the qualified doctors is very bad. It is a hard struggle for most of them to keep their bodies and souls together. In spite of the best intentions it has become impossible for them to practice good medicine. The crux of the problem lies in the poverty of the people, who are unable to meet the high and rising costs of modern medical care. Until the average income is substantially increased, first-class medical care will not be within the reach of the majority of people in the country. It is because of this poverty and the high cost that the politicians and governments are anxious to recognize all systems and even to encourage them.

## MEDICAL PROGRESS

## ELECTROENCEPHALOGRAPHY

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ADVANCES in electroencephalography have been so rapid that even for many who are actively engaged in the field, a survey of current status is the best account of recent progress. This is due largely to the fact that electroencephalography has both stimulated and implemented neurologic research by electric technics. The result has been a research that includes electroencephalography as an inseparable part and has elaborated many neurophysiologic and neuroanatomic novelties. At the same time there has been a steady accumulation of reports about the kinds of electroencephalograms associated with different mental or physical diseases. In this short survey the emphasis will be less on the latter than on the former set of advances in the field.

### Large Electric Fields and Unitary Neuronal Origins

Electroencephalography is a special part of general electrophysiology. The electroencephalogram, like the electromyogram and the electrocardiogram, is a sampling of electric fields. Its analogy to the electrocardiogram is especially close in some details. The electrocardiogram is a sampling of a large, complex and continuously varying electric field, which is distributed notably over the torso, where it is the net distribution of electric forces "generated" by the syncytial mass of the heart.[1] The electroencephalogram is a sampling of a large, complex and continuously varying electric field, which is distributed notably over the scalp, which can be resolved into a number of smaller component fields and which is attributed to the summated, synchronized, myriad and individually minute electric fields each of which attends the activity of a single neuron of the cerebral cortex.

The illustration[2] selected for this survey (Fig. 1) shows the reconstruction of such a field. The appearance of the reconstruction and the method of making it from a large number of samples are like the appearance and method of reconstructing fields which have been mapped on the torso for various phases of the cardiac cycle, and the similarity is significant enough to warrant the citation of references to work along these lines by Nahum et al.[1,3-5]

Interest in such fields has been steadily increasing. Their consideration is a necessary adjunct to the familiar criteria, perhaps exploited almost to exhaustion, of frequency, amplitude, contour and distribution of waves. They have been considered notably by Bishop,[6] Brazier,[7,8] Hunt and O'Leary[9] and Lilly[10] among many others.

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To explain the unitary neuronal origins of the large fields, it was at first more or less explicitly and generally assumed that brain waves were the envelopes of numbers of action potentials of the familiar kind that attend the transmission of nerve impulses. This assumption has now been almost and perhaps quite universally abandoned in favor of the assumption that brain waves are the slower and less familiar electrotonic potentials of the neurons. Electrotonic and action potentials can be recorded by many of the same procedures. Each action potential coincides in origin, course and termination with a nerve impulse. Electrotonic potentials do not have this same precise relation to the nerve impulse: they may be present when no impulse is being transmitted, they may arise as part of the preparation for an impulse, and they persist after its passage. As a crude analogy, action potential and electrotonus can be compared to the flaming and smoldering of tinder: the action potential corresponds with the quick, consuming flame, and the electrotonic potential with the slow smoldering, which may run its course without a flame or may prepare the way for a flame and linger after. In this connection Li, McLennan and Jasper[11] have said, "The most plausible hypothesis is that they [brain waves as recorded in electroencephalograms] represent synchronized oscillations in membrane potentials possibly involving small interneurons and dendrites in the cortical matrix, oscillations which would have a definite effect upon neuronal excitability, but [would] not [be] dependent upon neuronal discharge."

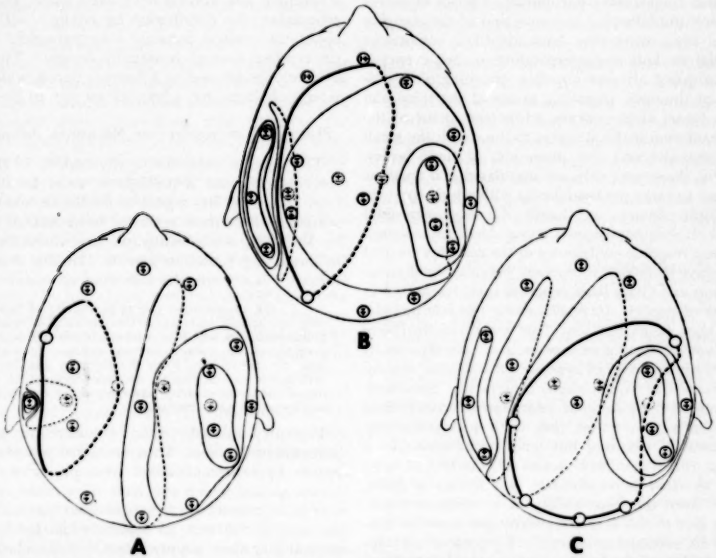


FIGURE 1. *Diagrams Representing a Continuously Changing Electric-Current Field at Three Different Moments. The diagrams were constructed from an electroencephalogram that showed runs of diffuse, regular waves at 3 per second and 50 to 75 microvolts. The field had two poles, one in the left temporal and one in the right central region. At one moment the left temporal region would be positive to the right central region; after a continuous change lasting one sixth of a second, the right central would be positive to the left temporal region; and so on alternatingly throughout each run of waves of 3 per second. Electrodes (represented by small circles) and equipotential lines are shown by solid inking over the convexity and by interrupted inking on the undersurface of the cerebrum. (The four basal electrodes[sp-111] lie between and roughly in line with the pinnas of the two ears: the interruption of the inking of the circles by which they are represented is not clear in the reproduction.) Very heavy inking is used to demonstrate the mean potential line, which was continuously changing in position, and the diagrams show the field during its roughly extreme left* (A), *intermediate* (B), *and right* (C) *positions. It is supposed that the field was created entirely by the synchronized activity of cortical neurons and that large pyramidal cells made the major contribution. Activity of the two hemispheres may have been synchronized by impulses through the corpus callosum or by impulses of the centrencephalic system. The patient was a woman in her sixties. Some years before the electroencephalogram, she had had an occlusion of the left middle cerebral artery. The lesion was confirmed at autopsy some time after the tracing was made.*

In the search for the unitary neuronal origins of such large electric fields Bishop and Clare[12] have studied the cat's optic cortex with microelectrodes. Using a jeweler's delicacy of technic and a mathematician's precision of reasoning, they have constructed, tentatively and with qualifications omitted from this fragmentary paraphrase, a series of events including the following sequence and in the complex cortical brain wave they have identified component potential oscillations corresponding to each event: in the first place afferent impulses, traveling along the axons of the optic radiation, arrive at the third and fourth layers of the cortex, where the axons of the optic radiation make synaptic contact with the small cells (granules and star pyramids) of these layers; secondly, these small cells are stimulated and transmit impulses to large pyramidal cells with which they are in synaptic contact; and, finally, the large pyramidal cells, with their conspicuous apical dendrites, respond and their response contributes to the complex cortical brain wave its largest component potential oscillation.

Bishop and Clare have reported their researches in a series of papers. In one[13] among the latest of the series they point out that "the elaborate flexibility of activity of the higher centers is . . . chiefly a matter of the complexity of available connections" among the neurons of which these centers are composed. For some of these complex interneuronal connections of the cat's optic cortex they offer a diagrammatic and carefully reasoned but tentative schema. In a perhaps rueful comment on this schema they observe that "its chief persuasiveness, not to say support, derives from the impossibility of its demonstration, due in fact to the very complexity presumed to constitute its essential property." To present an adequate and confidently accurate account of findings in this fundamental and very complex field of research is beyond the capacity of any but a specialist in the field, and I am not one.

Theoretical nerve nets[14,15] can be woven with varying degrees of exuberance. The schema constructed by Bishop and Clare represents a nerve net of simple design, and their comment on it is a sobering influence.

Finally O'Leary and Goldring[16] are probably predicting a new extension of electroencephalography when they say, "We now believe that the D.C. [direct current] changes are as expressive of neural process as the conventionally recorded forms of cortical activity." The conventionally recorded forms of cortical activity are currents varying at frequencies recorded as the waves of the familiar electroencephalogram. The direct currents of which they speak are cortical voltages, which vary so much more slowly that they cannot be recorded by the unmodified electroencephalograph. It is supposed that[16] "a significant component of cortical D.C. [direct current] potential arises from a polarization gradient along the exterior of the large pyramidal cells of the cerebral cortex and that this gradient is reflected in a difference of potential between cortical surface and subcortical white matter or ventricle." Again, the large pyramidal cells of the cerebral cortex figure as important unitary sources of its large electric fields. Later and elsewhere[17] they add that "though many theoretical assumptions have been made, knowledge concerning the distribution of changes within and about the cortical pyramid [the pyramidal cells of the cerebral cortex] is actually skimpy." They have evidently progressed to a frontier across which electroencephalographic advances are yet to be made.

### Electric Rhythmicity of Neuronal Aggregates

The regular character or rhythmicity of the electroencephalogram is perhaps its most familiar feature. More or less regularly oscillating electric potentials such as those recorded from cortical neurons by the electroencephalograph are characteristic of neuronal aggregates in general. In this connection Bremer[18] has made the following comment:

> . . . the spontaneous electrical activity of the brain is only one special instance of the tendency to synchronized autorhythmicity which is common to all the neuronal aggregates of the central nervous system. Studied in the most diverse objects, from the catenary ganglions of invertebrates to the human cerebral cortex, this "spontaneous" neuronal activity has everywhere shown the same oscillographic characteristics.

Partially isolated tissues continue to generate potential oscillations. Thus, sustained potential oscillations have been recorded from pieces of cerebral cortex around which cuts have been made in such a way as to transect all their neuronal connections with the rest of the nervous system while leaving their normal pial blood supply intact.[19,20] Regularly oscillating potentials have been recorded from sections of the spinal cord similarly prepared.[21] It is generally believed that these oscillating potentials arise spontaneously in the isolated tissues, though it has been asserted[22] that they occur only if the isolated tissues are stirred up by stimuli from the outside.

Different neuronal aggregates have their own distinctive forms of rhythmicity or oscillating potentials. For example, the occipital cortex generates alpha activity, strong beta activity is recorded from the motor cortex,[23] and Shinners has recorded alpha-like activity by applying electrodes directly to the thalamus of an anencephalic idiot.

The potential oscillations generated by a particular aggregate are modified by axonal impulses coming to that aggregate from other parts of the nervous system and by the interruption of such impulses. Bremer,[18] for example, transected the brains of cats between the superior and inferior colliculi and observed that the brain waves recorded from the cerebral cortex of such a *cerveau isolé* resembled those of normal sleep presumably because the transection had interrupted impulses that would otherwise have reached the cortex. Moruzzi and Magoun[24] transected the cat's

brain at the level of the first cervical segment. They recorded high voltage, slow, very regular oscillations from the cerebral cortex of such an *encéphale isolé* when it was unanesthetized and in a state of "relaxation"; when the reticular substance of its brain stem was stimulated by low-voltage, high-frequency electric shocks, the cortical activity that has just been described was replaced by lower voltage, faster, less regular activity; and from the whole body of their observations Moruzzi and Magoun conclude "that EEG changes seemingly identical with those in the physiological arousal reactions can be produced [in the cerebral cortex] by direct stimulation of the reticular formation of the brain stem." In the cerebral cortex of the cat Jasper and his associates[28] were "able to reproduce the bilaterally synchronous wave-and-spike complex of petit mal epilepsy by rhythmic electrical stimulation at 3 per second localized to a small region within the intralaminar nuclei of the thalamus near the anterior portion of the massa intermedia." And in the same passage Jasper goes on to say, "By implantation of stimulating electrodes within the mesial portion of the thalamus we have been able to reproduce not only the [cortical] electrographic picture, but also the clinical form of petit mal seizure in cats and monkeys." In recordings from the pyriform cortex of rabbits, MacLean and his associates[26] have shown the appearance or increased prominence of very regular, higher-voltage, slower oscillations in response to the animal's smelling something, tasting something or having its tail pinched hard.

Electroencephalographers have been especially interested in the idea that by reverberating circuits between thalamus and cerebral cortex these two structures in particular might influence each other in the way just described. Speaking notably of thalamus and cerebral cortex, with implicit reference to other pairs of structures, Bishop[6] has offered the following explanation:

> Each structure thus shows some ability to react without the influence of the other, but the activity of either will be altered by the action of the other upon it. The reciprocal influence between one structure and another, however, is not the same as a cyclic reverberation in which the excitation of one by the other is specific and essential. Rather, that interaction may be in terms of maintenance of a patterned, excitable state, either locus being dominant, and either capable of driving the other when its excitability level is raised to the threshold of spontaneous discharge. Reciprocal reverberation might thus become a special case of a more general relationship of corticothalamic interaction.

But, elsewhere in the same paper, Bishop says that, at least as of November, 1949, "no final or, to the writer, satisfactory evidence for true reverberation between thalamus and cortex has ever been offered (not to say accepted)."

Aggregates can be highly selective in their response to axonal impulses coming to them at regular frequencies, and in the two examples that follow, the frequencies to which the aggregates respond are close to spontaneous frequencies of the aggregates themselves. This is a commonplace where photic stimulation is concerned. Thus, to give an oversimplified example, flashes at 10 per second may be attended by strong occipital potential oscillations at the same frequency in a person whose normal alpha rate is at or near 10 per second whereas flashes at other frequencies are not attended by any visible effect. This selectivity was one feature of the important experiments performed by Dempsey and Morison,[27-29] which have contributed so much to current developments in electroencephalography. They worked with cats anesthetized by Nembutal. The electrocorticograms of cats thus anesthetized showed spontaneous bursts of waves at frequencies of 8 to 12 per second. Dempsey and Morison found that a series of regular electric stimuli applied to the dorsomedial region of the thalamus was followed by potential oscillations, which were widespread in the cortex:

> . . . [stimuli] applied at a rate slower than the 8 to 12 per second frequency of the spontaneous bursts usually set up a train of cortical potentials at this frequency, with the result that the stimuli applied at a rate markedly exceeding that of the spontaneous potential lead[s] to a complete breakdown of both the recruited and spontaneous bursts. Between these two extremes lies a band in which the recruited potentials may be driven accurately at frequencies only slightly greater than those of the spontaneous bursts.[29]

Arellano, Schwab and Casby[30] have shown a comparable selectivity in the response to pure tones.

There is presumably some positive relation between the oscillating potentials of an aggregate and the impulses going out from it to other parts of the nervous system. Thus, when a man is about to clench his fist or is beginning to clench it, the beta activity wanes in the fist region of the contralateral motor cortex and then waxes again whether he keeps his fist clenched or relaxes it.[25,31] It has also been said "that when alpha activity is present, there is a significant tendency for . . . voluntary movement to be initiated always at the same point in the phase of the alpha wave."[32]

The oscillating potentials and the random potentials that one can record from nerve tissue are modified by chemical changes, local or systemic and physiologic or nonphysiologic. Greville and Heppenstall,[33] writing as long ago as 1950, have said, "Even at this early stage, a formidable amount of literature concerned with the effects of drugs on the electrical activity of the brain has already accumulated . . . All these diverse researches have provided material for a new branch of pharmacology." The survey cited remains the best that has come to my attention. Unfortunately, it is not possible within the space of this review to include a survey of this "new branch of pharmacology." The temptation to mention work by Arduini and his associates[34] is, however, irresistible because of its relevance to what is yet to be said about epilepsy. To the cerebral cortex of the rabbit these investigators applied strychnine in amounts just sufficient to produce spiking potentials in the ani-

mal's electrocorticogram. They then subjected the animal to a variety of conditions and found that stimulation produced either one of two opposite effects. Sometimes it caused an aggravation of the spiking and sometimes a suppression. One is strongly reminded of the clinical phenomena of reflex epilepsy, of the apparent abortion of an epileptic patient's abnormal electric activity by the noise of a loud whistle,[25-27] and of the epileptic patient's common report that he can abort a seizure by an effort of the will or, less often, by some physical act like clenching his fist.

Space also precludes anything more than passing mention of the paroxysmal responses of the exposed cortex to direct electric stimulation and of the many and extensively investigated correlations between rhythmicity and age. Rhythmicity also varies with variations in physiologic status: its variations with sleep are an example[8] of which new and important features have been described by Schwab, Passouant and Cadhilac.[38]

How such autorhythmicity is maintained within relatively smaller and relatively larger aggregates of neurons is a concern of current speculation and research. Lorente de Nó[39] proposed the occurrence of nerve impulses circulating in reverberating closed chains of a few self-re-exciting neurons. The self-sustained nervous activity in such a smallest-sized aggregate of neurons would be like the activity in the nervous system of the jellyfish, which "has neither brain nor ganglia" and which finds "a nerve net of simple cells . . . adequate for all its needs, the same convulsive message being repeated over and over again . . . : push, push, push."[40] But in controversion of this attractive picture of the smallest-sized neuronal aggregate that is sufficient for self-sustained activity, Li and his associates,[11] speaking on the basis of their research, have said, "There is no support for the notion that the 'spontaneous' rhythms of the brain are due to nerve impulses circulating in reverberating closed chains of self-re-exciting units, since the slow waves continue when unit discharge (at least as recorded with microelectrodes) is suppressed by hypoxia or anesthesia."

In contrast to such possible smallest-sized neuronal aggregates in which self-sustained rhythmicity might occur, the possibility that the thalamus and cerebral cortex interact with each other to form a larger aggregate in which rhythmical activity might be self-sustained has already been considered. And here one must drop the subject, with memories of the authoritative skepticism that has been quoted about this possibility too — a skepticism to which Bremer,[41] in his turn, has given more recent expression.

## New Neuronal Avenues

In the research of which electroencephalography has become an inseparable part, a general procedure has been to stimulate the nervous system at one point, to observe the electric response at another point and to investigate the neuronal avenues by which impulses can travel from the first point to the second. Sometimes, the results agree with and sometimes they are at odds with already established anatomic knowledge.

As an instance of this procedure, strychnine is applied to a small part of the cerebral cortex, and a study is made of the electric responses arising both where the strychnine has been applied and elsewhere. This is the "physiological neuronography" of Dusser de Barenne,[42] and "most of our present knowledge of cortical and subcortical connections is due to this method."

An early and important object of such a study was an effect that Derbyshire and his associates first reported from the laboratory of Dr. Alexander Forbes at the Harvard Medical School and is designated here, in accordance with a common usage, by the name and variations of the name, "Forbes's secondary response."[43-47] The references provide for the subject a coherent bibliography not readily found elsewhere. This secondary response of Forbes, first observed as a remarkable effect in deeper stages of Avertin and Pentobarbital anesthesia and in asphyxia, was a conspicuous response of the cat's cerebral cortex to stimulation of the sciatic nerve under these conditions. It appeared simultaneously in both cortexes after stimulation of either sciatic nerve and was obtained equally well in all regions of both cortexes. Between stimulus and response there was an interval, distinctively long for such effects, of 30 to 80 milliseconds. For impulses giving rise to Forbes's secondary response, different stretches of the following unexpected itinerary are variously possible, probable or certain: after stimulation of the right sciatic nerve impulses travel centralward through the right sciatic nerve into the right side of the spinal cord and rostralward in the cord; somewhere below the level between superior and inferior colliculi, impulses divide into two sets, one set continuing in the right side of the spinal cord and brain stem, and the other going across from the right into the left side of the spinal cord or brain stem and to the left cerebral cortex. The latter are the first of two sets of impulses that cross from right to left. The impulses that continue in the right side travel probably in the medial division of the medial lemniscus; they course through the midbrain and, probably staying entirely outside the thalamus, through the dorsal and medial part of the subthalamus to the region of the anterior pole of the right amygdala, whence they are widely distributed (apparently over direct paths) to the right side of the cerebral cortex. In addition to the right-sided impulses just described as reaching the right side of the cerebral cortex, there are right-sided impulses that cross from the right hemisphere, but not from the right side of the cerebral cortex, through the anterior third of the corpus callosum, into the left

hemisphere, where they make connections with structures deep in the left temporal lobe and thence are distributed to the left side of the cerebral cortex. These are the second of the two sets of impulses that cross from right to left. Finally, a "spontaneous cortical rhythm made up of widely separated large waves similar in appearance to the secondary discharge may also . . . arise in this temporal area and be synchronized throughout the cortex by means of the conducting system outlined for the secondary discharge."[44] And so rhythmicity recurs.

Impulses created by stimulation of the left sciatic nerve follow an itinerary that is the mirror image, on a reflecting surface in the medial sagittal plane, of the itinerary just given for impulses created by stimulation of the right sciatic nerve.

In the preceding account of these new neuronal avenues there are gaps because "just what fibers form the path for the secondary response is difficult to determine." The account has seemed worth giving here because the avenues are so surprising and because they are, though clearly reported, nowhere clearly summarized in the primary sources and are neglected in at least some secondary sources.

"The nonspecific afferent system" is a novel term now, with its variants, well established as the name for another set of new neuronal avenues that have more immediately apparent clinical significance and have been explored even more recently than the avenues for Forbes's secondary response. The term is related by contrast to the "specific afferent system," which designates familiar avenues each of which is specific for the impulses subserving one or more distinct sensations (for example, touching, hearing, seeing and tasting) as those impulses course from periphery through thalamic and related nuclei (posterior ventral, medial geniculate, lateral geniculate and innermost part of posterior ventral nuclei of thalamus respectively for the examples cited) to distinct parts of the cerebral cortex (postcentral, superior temporal, calcarine and, again, apparently, postcentral parts respectively for the examples cited).

Details of the nonspecific afferent system are still the object of lively research and debate. The reader who would grasp developments past and future will have more use for an outline of these avenues that is mistaken and precise than for an outline that escapes mistakes by a bewildering prolixity of detail or an enfeebled vagueness. Such a mistaken and precise outline, constructed mainly from papers by French and his associates[48] and by Starzl and his associates,[49] follows.

The nonspecific afferent system begins in the reticular formation and periaqueductal gray matter of the brain stem. As far as they have been studied, all afferent systems including the specific sensory channels (for instance, somatic, auditory, visceral from the splanchnic nerves, visual, vagal and olfactory) contribute impulses to the beginning of the nonspecific afferent system — that is, to the reticular formation and periaqueductal gray matter of the brain stem. Presumably, the impulses arrive through collaterals from the specific afferent fibers to the neurons of the polysynaptic nonspecific afferent system.

*(To be concluded)*

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## MEDICAL INTELLIGENCE

# PRESACRAL CHORISTOMA IN AN ADULT

GERALD LEWIS HAIDAK, M.D.,* AND WILLIAM BATES, M.D.†

PHILADELPHIA

AN extensive review of the literature concerning presacral teratoid tumors shows this type of lesion to be fairly unusual. Approximately 75 case reports are on record dating from 1831. Most of these reports deal with complications of various types — urinary retention (Brown and Brown[1]) or rectal displacement (Walker[2]), and a few with abscess formation (Brown and Brown[1]). Pack[3] speaks of the rareness of malignant change in these lesions. However, all reports reviewed dealt with newborn or young children. Ravitch and Smith[4] report a case in a thirteen-year-old girl. In the case reported below, although there were manifestations of backache at an earlier age, there were no clear-cut symptoms until the age of twenty-one, and the patient was considered to have a common pararectal abscess for thirteen years with 9 admissions to different hospitals. Moreover, this case had the unusual feature of showing a single type of misplaced tissue, instead of the usual varied structures seen in presacral teratomas. Thus, it fits the definition of a choristoma — namely, the growth to tumor proportions of a misplaced embryonal remnant. In this case misplaced respiratory epithelium was responsible.

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It is not our intention to present an exhaustive review of the literature. The reports already mentioned,[1,4] as well as that of Gross et al.,[5] cover the literature on the subject and are recommended for reference.

### CASE REPORT

M.D.M., a 34-year-old tie maker, entered the hospital with the chief complaints of an ache in the lower back, nervousness and profuse purulent rectal discharge. The family history was noncontributory. She had fallen on her back at the age of 8, with the resultant severe backache. She was studied at another hospital at that time. The menstrual history was normal.

The patient was confused and anxious (a sister was also a source of the information obtained in the history). Thirteen years previously a frequently recurring (14 times) painful pararectal swelling began, requiring incisions and drainages with diagnosis of pararectal abscess. The drainage was purulent, profuse and continuous. Ten years before admission there had been a severe hemorrhage from the rectum. At that time she was admitted to another hospital, where both rectal and abdominal operations were performed. Symptoms of purulent pararectal drainage persisted. Two years later, after another episode of rectal bleeding, she was again hospitalized, but operation was not performed. About 3 months before admission she was again studied at another institution, where x-ray examination of the spine was negative. She still complained of severe low-back pain.

About 3 weeks before admission the pain in the lower back became unbearable. The patient began to have sweating and low-grade temperature fluctuations. The pain was very severe, requiring large doses of analgesics and sedatives (morphine, 0.12 to 0.15 gm. daily). This illness was accompanied by nervous manifestations of tenseness, excitement and anxiety (toxic psychosis). She stated that there was pain in the lower sacrum, radiating to both buttocks (especially on the right) and both thighs. There was a copious, purulent rectal drainage.

Physical examination showed a woman in acute apparent distress, who actually screamed continuously, moved about in bed violently and required restraints. She was sedated with heavy doses of barbiturates but was still very uncooperative. The examination, which was performed with difficulty, was negative except for severe tenderness and swelling of both buttocks and a profuse purulent drainage from the anus.

The temperature was 104°F. by rectum, and the pulse 120. The blood pressure was 140/60.

Laboratory studies were not remarkable and were consistent with infection. X-ray examination of the chest and spine was negative. The patch test was positive.

On the 4th hospital day sigmoidoscopy under anesthesia revealed normal mucosa to a level of 5 or 6 cm. above the

mucocutaneous junction, where an indurated fluctuant mass on the posterior wall was noted. A longitudinal incision was made at this level, and a large quantity of purulent material was expressed. A mass was located in the retrorectal space and incompletely excised.

Microscopical examination showed a cyst lined by pseudostratified, ciliated columnar epithelium. The wall of the cyst was fibrous tissue in which a few mucous glands and a few small particles of bone were seen.

Subsequently, the patient improved with antibiotics and seemingly adequate drainage. However, by the 14th postoperative day, the right and — to a lesser degree — the left buttock had become obviously enlarged and fluctuant. Needle biopsies in attempts to aspirate fluid from the buttocks were repeatedly unsuccessful. Later that day, the right buttock was extensively opened transversely down through the gluteus muscles, and a vast lake of pus was encountered. The left buttock was treated similarly but less extensively.

The areas were carefully débrided and excised, the extensions explored, and presacral and postsacral ramifica-

FIGURE 1. *Microscopical Section of a Specimen Removed at Operation.*

tions found; these were also débrided and excised. It was noted that the coccyx was fractured and that a spicule of bone extended into the rectum, suggesting the avenue of secondary invasion. The anterior surface of the sacrum was much eroded. It was believed that all the tumor had been excised.

The entire operative site was packed with gauze, and rubber tubes inserted for drainage. All the specimens taken from various sections of the operative site showed teratoid (choristoma) tumor. Streptokinase and streptodornase solutions were used daily as adjuvant therapy to complete the débridement. The patient had a slow but uneventful recovery with complete healing.

Microscopical study of the sections showed well differentiated, pseudostratified, ciliated columnar epithelium, which at certain points appeared to have undergone squamous metaplasia (Fig. 1). In the stroma underlying this epithelium there was a considerable infiltration of lymphocytes and plasma cells. Skeletal muscle and mature bone were also noted. There was no histologic evidence of malignant change. The appearance of this tissue was strongly reminiscent of the lining of the upper respiratory tract.

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## DOCTORS AFIELD

### Henry Dearborn


HOWARD N. SIMPSON, M.D.

SPRINGFIELD, MASSACHUSETTS


TOWARD the end of his life Thomas Jefferson wrote to an old friend, the man who had been his secretary of war for eight years: "Man, like the fruit he eats, has his period of ripeness. Like that, too, if he continues longer hanging to the stem, it is but a useless and unsightly appendage." The friend was Henry Dearborn, for whom Fort Dearborn was named, and whom history has dismissed with a paragraph because, as senior major general, his inactivity and inefficiency contributed measurably to the ineffectiveness of American land forces in "Mr. Madison's War." The words were unintentionally ironic because Dearborn's tragedy was in hanging too long to the stem; his period of ripeness was one of gallantry and high honor.

He was born in Hampton, New Hampshire, in 1751. At the age of twenty-one, having studied medicine under Dr. Hall Jackson, of Portsmouth, he began his practice in Nottingham. The drums that beat at Lexington and Concord three years later, however, called Dr. Dearborn afield — for the rest of his life. He organized a company of militia, and, as its captain, marched his 60 men to Cambridge, where the outfit was incorporated into the regiment of the temperamental Colonel John Stark to fight at Bunker Hill. Three months later he volunteered to go with Arnold to Quebec; in his journal he left a vivid account of that heroic and hapless march:

> November 1 This morning we new Pitched our Canoe she being Somewhat Leaky, we have run several times on the Rocks going down falls, where I expected to have Stove her to pieces, we put her in and proceeded down the river, which Remains very rapid, and a Bounding in falls, we got down a Bout 30 Miles, by which time our Canoe got to be worn out, we went on shore and Encamp'd, Here I Saw Some of the foot-men who were almost Starved, This day Capt. Goodrich's Company Kill'd my Dog, and another dog, and Eat them, I remain very unwell.

A few days later his illness worsened ("I was this time in a High fever"), and he was compelled to drop behind his troops. He recovered, however, in time to rejoin his men for the assault on Quebec, was captured, made a prisoner of war, paroled and finally, more than a year later, exchanged. He became a major, ultimately in charge of the First New Hampshire Regiment, and distinguished himself in the campaigns of that autumn in upper New York. The *Journal* for October 17, 1777 strikes an exultant note: "17th this Day the Great Mr Burguoyn with his whole Army Surrendered themselves as Prisoners of war with all their Publick Stores, & after Grounding their armes march.d of for New England, the greatest Conquest Ever known." For a former prisoner of war, it must have seemed just that. But the triumph

was short-lived. There was little to eat on Thanksgiving, and "Crismus" at Valley Forge was spent in a dismal rain. Later in the war his regiment won commendation from General Washington for its conduct at Monmouth; he campaigned with Sullivan in the Wyoming valley, and he was in at the kill, as a member of Washington's staff, at Yorktown.

He was discharged from the Army in 1783 and went to live in Kennebec County, Maine, where he became United States marshal for the district. He served two terms in the House of Representatives from the district, which was then part of Massachusetts, and in 1801 Jefferson appointed him secretary of war. It seems to have been fashionable, when the republic was young, for doctors to become secretaries of war and have forts named after them. McHenry, Dearborn and Eustis followed the pattern, so that, except for a frantic interval of nine months during which there were 3 lay incumbents, the War Department was headed by a physician for seventeen years. The record they made does not render imperative the revival of the custom. Most of Dearborn's official duties during this period seem to have revolved around matters concerning the Indians. It is scarcely to his discredit that the nation had already embarked on a policy of "in time of peace prepare for nothing." In 1809 he became collector for the port of Boston, but in 1812 President Madison did him the great disservice of making him senior major-general in the United States Army. For Madison, who admired his former fellow cabinet member, it seemed like a good choice. Dearborn was politically harmless, but more important, he was a New Englander, and New England was sitting this one out.

This time it was different. Dearborn was sixty-one and fat, and had rheumatism. The spark was gone. The war was different too. The onrushing sweep of history had made the Revolution inevitable. This brawl could and should have been stopped by half a dozen men around a table. As a matter of fact Dearborn, without authority and without success, attempted to stop it.

In the fall of 1812 he led from Plattsburgh what was intended to be a campaign against Montreal, but his troops, composed principally of militia, are said to have refused to cross the border. One of the surgeons of the expedition, William Beaumont, for whom immortality was lying in wait, gives a revealing sidelight on the situation:

> Near the middle of November the Army moved from Plattsburgh to the Province Line, 45 Deg. North, taking no tents, and destitute of covering, save a Blanket or two, lying out in open air after marching all day through the mud and water, and thus exposed to the inclemancies of the weather for a week, encampt in the woods. After which the army returned to Plattsburgh, and there encamp'd again in the woods without Tents or Huts the first night, which was very rainy and cold: the Second also was wet and windy. They then moved to Saranac, and encamped again in the woods, during which time the weather was very various—warm and cold, sometimes raining, sometimes snowing—the men lying upon the cold, wet ground, with only a fire before their tents, for two, three or four weeks. Whilst in this wretched and deplorable situation, the men were seized with Dysentery, Intermittents, Pleurisy, Peripneumony, Cynanche and Rheumatism, which made the very woods ring with coughing and groaning.

In the following year Dearborn's command captured York (now Toronto) and burned it, thereby suggesting a similar maneuver to the British when Washington later fell into their hands. His triumphs were trivial compared to his disasters, and he was relieved of his command in July, 1813. After the war he served for two years as minister to Portugal and then retired to Roxbury, where he died in 1829.

It is hardly surprising that his record as a field general was poor. A full generation earlier he had been a courageous and resourceful combat officer in charge of a handful of troops. His subsequent experience was as a civilian. It was not the background for a supreme commander. Perhaps in the bitterness of his last years he was able, sometimes, to forget the more recent failures and to picture again in his mind the young captain, swinging down from New Hampshire with his little band, dreaming of glory, yet never dreaming that the bright rosters of Bunker Hill, Quebec, Saratoga, Valley Forge, Monmouth and Yorktown would someday bear his name, or that a military outpost, named for him, would be the site on which would rise one of the great cities of the world.

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# CASE RECORDS
## OF THE
## MASSACHUSETTS GENERAL HOSPITAL

**Weekly Clinicopathological Exercises**

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

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## CASE 41011

### PRESENTATION OF CASE

A fifty-eight-year-old man was admitted to the hospital because of "shooting" abdominal pain of two months' duration.

Two and a half years previously intermittent pain developed in the midepigastrium when he was hungry, was not severe and was relieved by food and milk. After a year he consulted his physician, who demonstrated a "peptic ulcer" by x-ray examination and placed him on a regimen including a six-meal bland diet, antacids, belladonna and cessation of smoking. Adhering to this program, he became symptom free within three months. Over the ensuing several months he gradually liberalized his diet, discontinued medications and resumed smoking, with no recurrence of the previous symptoms. He remained perfectly well until three months before entry, when there was a gradual onset of constant dull pain in the left anterior flank just above the iliac crest. This did not seem to be related to meals. Two months later, when he again consulted his physician, an upper gastrointestinal series was negative, and a barium-enema examination revealed only a small polyp in the lower colon, which was later removed by cauterization endoscopically. About a week after the barium-enema examination he was awakened one night with excruciating "shooting" abdominal pain, which seemed to be predominantly in the lower abdomen and was thought to arise in the left midflank, radiating upward to involve the entire abdomen. No such episodes had ever occurred previously. The pain was described as both sharp and crampy. He continued to have attacks of variable severity almost daily until admission. There was no associated vomiting. The pains were often accompanied by perspiration and at night often prevented sleep. In the intervals between the episodic bouts of severe pain he was plagued by constant, nagging, dull, left-flank pain. For two months he had also experienced severe constipation, which was for him a distinct change. Even with laxatives his stools remained hard, and bowel movements occurred every two or three days. There was no history of melena. During the last six weeks of the illness there was marked anorexia along with a 30-pound weight loss. Four weeks before entry he was admitted to another hospital, where a complete work-up, including a gastrointestinal series, failed to demonstrate any abnormalities. At no time during the illness had he been aware of jaundice.

The past history revealed that on two occasions, thirty-six and thirty-three years before admission, he had been treated conservatively for "appendicitis." A left herniorrhaphy and ligation of varicose veins of the left leg were performed thirty and two years previously respectively. He had had minimally productive cough for three months and nocturia (two or three times) for many years.

Physical examination revealed a well developed, well nourished man who appeared youthful and vigorous and in no obvious distress. Examination of the heart and lungs was negative. One observer described slight guarding of the abdomen, without spasm, minimal deep tenderness in the left flank anteriorly and a nontender liver edge, which descended 1 fingerbreadth below the right costal margin on deep inspiration. Other observers were unable to corroborate these findings and described the abdomen as entirely normal to palpation. All agreed that no masses were palpable. A few small nontender lymph nodes were felt in each axilla. Rectal examination revealed a few hemorrhoids. The prostate was moderately enlarged but normal in consistence. Neurologic examination was negative.

The temperature was 97°F., the pulse regular at 74, and the respirations 20. The blood pressure was 150 systolic, 80 diastolic.

Urinalysis was negative. The hemoglobin was 14.2 gm. per 100 cc., and the white-cell count 11,300, with 72 per cent neutrophils, 15 per cent lymphocytes, 1 per cent monocytes, 1 per cent basophils, 10 per cent eosinophils and 1 per cent unclassified cells. The sedimentation rate was 13 mm. in one hour. A blood Hinton test was negative, as was a stool guaiac test. An electrocardiogram was interpreted as being within normal limits. A barium-enema examination and an intravenous pyelogram were considered negative. An upper gastrointestinal series was negative except for some prominence of the gastric folds. The stomach emptied promptly, and serial films of the small bowel were normal. A cholecystogram was reported as normal. X-ray films of the lumbosacral spine were reported as showing slight posterior narrowing of the fifth lumbar intervertebral space along with mild degenerative changes and spurring of the lumbar spine.

The patient was placed on a peptic-ulcer regimen, without any clinical change. Proctosigmoidoscopy to

20 cm. was negative except for hemorrhoids and a small papilloma at the internal sphincter. A consulting orthopedist could elicit no abnormalities on physical examination but on review of the x-ray films of the spine believed that there was slight compression of the bodies of the second and third lumbar vertebras. A surgical consultant noted prominence of a collateral venous pattern over the abdominal wall. This was evident bilaterally, extending from the deep epigastric to the intercostal and mammary vessels. Despite hot fomentations to the abdomen and bed boards there was no change in the patient's status. During the fifteen days after entry there were at least four episodes of severe abdominal pain. Examination during these bouts revealed the patient to be active and grunting with pain. The abdomen was not tender, but voluntary spasm involved most of the abdominal musculature. The acute episodes of pain were occasionally partially relieved by atropine alone but at other times necessitated 50 mg. of Demerol in addition. A morphine-neostigmine test carried out in the interval between acute episodes (10 and 1.0 mg., respectively, being administered subcutaneously) failed to elicit any increase in abdominal pain. The pre-test level of serum amylase was 12 Russell units, and at four hours it was 20 units per 100 cc. A previous amylase determination had been 21 units per 100 cc. A gastric analysis revealed 5 units of fasting free acid and 110 units one hour after histamine. The gastric content was guaiac negative. The alkaline phosphatase was 9.3 Bodansky units per 100 cc. A bromsulfalein test showed 6 per cent retention of the dye at forty-five minutes. A test for urinary porphyrobilinogen was negative. The fasting blood sugar was 114 mg. per 100 cc. The first attempt at a glucose tolerance test was unsuccessful since the patient vomited after ingesting the test dose; this was apparently the only episode of vomiting that had occurred during the hospital course. A later test was successful and showed a fasting level of 111 mg. and subsequent levels of 142, 210, 160 and 138 mg. per 100 cc. at half an hour, one hour, two hours and three hours respectively. Stool guaiac tests on two occasions after admission remained negative. The patient continued to be constipated. The weight dropped to 145 pounds, and there was no change in the status of the symptoms of the present illness. The temperature remained normal except for a rise to 99.4°F. on the eleventh and twelfth hospital days.

An operation was performed on the seventeenth hospital day.

### Differential Diagnosis

Dr. Myles P. Baker*: The problem is one of the cause of abdominal pain that had been dragging and constant for two months and had been featured by severe exacerbations for about three weeks. I am surprised that a pain as severe as this was described could have been relieved by 50 mg. of Demerol. This man, who at times had periods of acute pain, had no localized tenderness, no abdominal mass and no involuntary spasm. He had been growing worse, had been anorectic and had lost 30 pounds of weight within two months. There were remarkably few objective abnormal findings on physical examination. The one finding that stands out is the surgeon's observation of the development of a collateral venous supply along the flanks, presumably with the blood passing upward from the epigastric to the mammary vessels. In the laboratory work there was little in the way of positive findings — a somewhat elevated alkaline phosphatase, an inability to raise the blood amylase levels after morphine and neostigmine and a glucose tolerance test that was "diabetic" in the absence of glycosuria. There was a noteworthy absence of anemia. The x-ray examinations, which were done in an attempt to localize the cause of the pain, turned up virtually nothing. There was no evidence of a malignant lesion in the stomach, no lesion in the small intestine, no gallstones, no evidence of extrinsic pressure on the stomach or transverse colon, as with a mass in the pancreas, and no signs of diverticulitis or tumor in the large bowel. Nor was there any evidence of kidney tumor; there was no reason to suspect from the examination of the urine that the left kidney was involved in this man's pain. There seems to have been some question about the soundness of a couple of lumbar vertebras, but it is hard to see how that would account for such a pain as the patient described. Did the radiologist see any positive findings on the x-ray films?

Dr. C. C. Wang: No.

Dr. Baker: Was a chest film done?

Dr. Wang: I do not believe so.

Dr. Baker: Have you any films that show the right leaf of the diaphragm?

Dr. Wang: Yes; the right leaf of the diaphragm as seen in the abdominal film is not elevated.

Dr. Baker: Was there any obvious enlargement of the liver?

Dr. Wang: No; there is no significant enlargement.

Dr. Baker: Because of these negative x-ray examinations and persistence of steady pain with serious exacerbations, those in attendance must have wondered whether the cause of the pain really lay outside a structure amenable to x-ray study. Could this man have had an aneurysmal dissection, or leakage from a saccular aneurysm of the abdominal aorta? I know that such persons do have pain, and I assume that, if there is hemorrhage into the retroperitoneal space with the formation of a large hematoma, there might be episodes of severe pain such as he had, but I should think that the course would have been punctuated by more evidence of circulatory collapse. One thinks of a thrombotic process in the inferior vena cava, but such a lesion, for which there was no antecedent or

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corroborative reason, would probably not have produced such pain as this man had. If I can consider the presence of collateral venous distributions on the abdominal wall as really present and of important degree, attention turns toward some disease that produced pressure on the inferior vena cava or actually invaded it and that very finding alone tends to militate against the diagnosis of abnormal aortic disease.

What sort of retroperitoneal malignant lesion could produce pain and possibly some obstruction to the inferior vena cava without giving x-ray evidence? I think of a primary malignant process in the body and tail of the pancreas or a primary retroperitoneal tumor such as lymphosarcoma or possibly sarcoma arising from the connective tissue in the retroperitoneal space. One might think, with this evidence of new venous channels in the abdominal wall, that one should consider the possibility of thrombosis of the inferior vena cava from one of its more frequent causes — namely, hepatoma, producing as it occasionally does, Chiari's syndrome with thrombosis in the vena cava as well. But there was very little evidence for such a diagnosis: the liver was not enlarged, and there was no ascites — two prime requirements for Chiari's syndrome.

Cancer of the body of the pancreas is not uncommonly found in such cases of abdominal pain that is unexplained by preoperative diagnostic maneuvers. It seems to me a plausible diagnosis here. Such a lesion is known to press upon or actually invade the inferior vena cava, with thrombus formation, and may produce such evidence of obstruction as this man apparently had. The fact that he had been losing weight and had been anorectic is quite in keeping with the diagnosis. The absence of some of the more common findings in cancer of the pancreas does not exclude such a diagnosis: certainly not the absence of jaundice, which is present in only about 20 or 25 per cent of cases of cancer of the body of the pancreas; and certainly not ascites, which is a late development. An epigastric mass was found only in about 1 out of 3 in one such series of cases. The absence of x-ray findings — of an extrinsic mass pressing on the stomach or on the transverse colon — is all too characteristic. The patients with cancer of the body of the pancreas may have a diabetic glucose tolerance test and the absence of sugar in about as many as 15 per cent. Pain in the left lower quadrant has been noted in perhaps 5 per cent of the cases. The result of the morphine-neostigmine test is inconclusive to my mind. It simply means that in this case the increase in muscle spasm and pancreas ferment secretion, which morphine and neostigmine may produce, did not occur. I should hesitate very much on this one test to make a diagnosis of extensive neoplasm that replaced pancreatic tissue.

It certainly is a possibility that I am dealing with something like a retroperitoneal lymphosarcoma, with pressure on or even invasion of the inferior vena cava, but my first bet is cancer of the body of the pancreas.

DR. BENJAMIN CASTLEMAN: Dr. Kranes, would you make a different diagnosis, or would you agree with Dr. Baker?

DR. ALFRED KRANES: His diagnosis seems like a very reasonable one to me.

DR. PERRY CULVER: Dr. Baker arrived at the same diagnosis that we eventually considered, but he based his reasoning on a better understanding of the possible significance of altered vascular anatomy that might have been present. Unfortunately, we disregarded the abdominal veins. This man was a very robust, jovial extrovert who appeared the picture of health and had kept his hospital roommates in a happy state. He was supposed to have lost 30 pounds of weight, but when we looked at him we could see no signs of weight loss. He had a completely negative work-up, and we wondered whether he was malingering. What finally impressed us were the facts that these pains awakened him at night and that he had weighed 190 previously but now weighed only 155 pounds. We had to believe his story of weight loss in spite of the way he looked. He also assumed a bizarre and characteristic posture whenever he had pains — that is, he lay in bed and put his foot up in the trapeze to relieve the pain. Putting these facts together with the knowledge that back or retroperitoneal pain relieved by bizarre posture in a so-called psychoneurotic patient should cause suspicion of cancer of the pancreas, we did certain tests as listed in the protocol. We placed a great deal more emphasis on these tests than Dr. Baker did, but perhaps his reasoning was more logical than ours. The fasting blood sugar of 114 mg. per 100 cc., a slightly elevated alkaline phosphatase, a slightly elevated bromsulfalein retention and a serum amylase that was just above the normal limits made us suspect disease in the pancreatic and biliary tracts. The diabetic glucose tolerance test was enough more positive objective evidence to make us all agree that a surgical exploration was indicated.

### CLINICAL DIAGNOSIS

?Carcinoma of body and tail of pancreas.

### DR. MYLES P. BAKER'S DIAGNOSIS

Carcinoma of body of pancreas.

### ANATOMICAL DIAGNOSIS

*Adenocarcinoma of pancreas, with metastasis to liver.*

### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The operation was done by Dr. Gordon A. Donaldson; he is not here, but Dr. Rodkey will tell us what was found.

20 cm. was negative except for hemorrhoids and a small papilloma at the internal sphincter. A consulting orthopedist could elicit no abnormalities on physical examination but on review of the x-ray films of the spine believed that there was slight compression of the bodies of the second and third lumbar vertebras. A surgical consultant noted prominence of a collateral venous pattern over the abdominal wall. This was evident bilaterally, extending from the deep epigastric to the intercostal and mammary vessels. Despite hot fomentations to the abdomen and bed boards there was no change in the patient's status. During the fifteen days after entry there were at least four episodes of severe abdominal pain. Examination during these bouts revealed the patient to be active and grunting with pain. The abdomen was not tender, but voluntary spasm involved most of the abdominal musculature. The acute episodes of pain were occasionally partially relieved by atropine alone but at other times necessitated 50 mg. of Demerol in addition. A morphine-neostigmine test carried out in the interval between acute episodes (10 and 1.0 mg., respectively, being administered subcutaneously) failed to elicit any increase in abdominal pain. The pre-test level of serum amylase was 12 Russell units, and at four hours it was 20 units per 100 cc. A previous amylase determination had been 21 units per 100 cc. A gastric analysis revealed 5 units of fasting free acid and 110 units one hour after histamine. The gastric content was guaiac negative. The alkaline phosphatase was 9.3 Bodansky units per 100 cc. A bromsulfalein test showed 6 per cent retention of the dye at forty-five minutes. A test for urinary porphyrobilinogen was negative. The fasting blood sugar was 114 mg. per 100 cc. The first attempt at a glucose tolerance test was unsuccessful since the patient vomited after ingesting the test dose; this was apparently the only episode of vomiting that had occurred during the hospital course. A later test was successful and showed a fasting level of 111 mg. and subsequent levels of 142, 210, 160 and 138 mg. per 100 cc. at half an hour, one hour, two hours and three hours respectively. Stool guaiac tests on two occasions after admission remained negative. The patient continued to be constipated. The weight dropped to 145 pounds, and there was no change in the status of the symptoms of the present illness. The temperature remained normal except for a rise to 99.4°F. on the eleventh and twelfth hospital days.

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Dr. Wang: I do not believe so.

Dr. Baker: Have you any films that show the right leaf of the diaphragm?

Dr. Wang: Yes; the right leaf of the diaphragm as seen in the abdominal film is not elevated.

Dr. Baker: Was there any obvious enlargement of the liver?

Dr. Wang: No; there is no significant enlargement.

Dr. Baker: Because of these negative x-ray examinations and persistence of steady pain with serious exacerbations, those in attendance must have wondered whether the cause of the pain really lay outside a structure amenable to x-ray study. Could this man have had an aneurysmal dissection, or leakage from a saccular aneurysm of the abdominal aorta? I know that such persons do have pain, and I assume that, if there is hemorrhage into the retroperitoneal space with the formation of a large hematoma, there might be episodes of severe pain such as he had, but I should think that the course would have been punctuated by more evidence of circulatory collapse. One thinks of a thrombotic process in the inferior vena cava, but such a lesion, for which there was no antecedent or

*Physician, Massachusetts General Hospital.

corroborative reason, would probably not have produced such pain as this man had. If I can consider the presence of collateral venous distributions on the abdominal wall as really present and of important degree, attention turns toward some disease that produced pressure on the inferior vena cava or actually invaded it and that very finding alone tends to militate against the diagnosis of abnormal aortic disease.

What sort of retroperitoneal malignant lesion could produce pain and possibly some obstruction to the inferior vena cava without giving x-ray evidence? I think of a primary malignant process in the body and tail of the pancreas or a primary retroperitoneal tumor such as lymphosarcoma or possibly sarcoma arising from the connective tissue in the retroperitoneal space. One might think, with this evidence of new venous channels in the abdominal wall, that one should consider the possibility of thrombosis of the inferior vena cava from one of its more frequent causes — namely, hepatoma, producing as it occasionally does, Chiari's syndrome with thrombosis in the vena cava as well. But there was very little evidence for such a diagnosis: the liver was not enlarged, and there was no ascites — two prime requirements for Chiari's syndrome.

Cancer of the body of the pancreas is not uncommonly found in such cases of abdominal pain that is unexplained by preoperative diagnostic maneuvers. It seems to me a plausible diagnosis here. Such a lesion is known to press upon or actually invade the inferior vena cava, with thrombus formation, and may produce such evidence of obstruction as this man apparently had. The fact that he had been losing weight and had been anorectic is quite in keeping with the diagnosis. The absence of some of the more common findings in cancer of the pancreas does not exclude such a diagnosis: certainly not the absence of jaundice, which is present in only about 20 or 25 per cent of cases of cancer of the body of the pancreas; and certainly not ascites, which is a late development. An epigastric mass was found only in about 1 out of 3 in one such series of cases. The absence of x-ray findings — of an extrinsic mass pressing on the stomach or on the transverse colon — is all too characteristic. The patients with cancer of the body of the pancreas may have a diabetic glucose tolerance test and the absence of sugar in about as many as 15 per cent. Pain in the left lower quadrant has been noted in perhaps 5 per cent of the cases. The result of the morphine-neostigmine test is inconclusive to my mind. It simply means that in this case the increase in muscle spasm and pancreas ferment secretion, which morphine and neostigmine may produce, did not occur. I should hesitate very much on this one test to make a diagnosis of extensive neoplasm that replaced pancreatic tissue.

It certainly is a possibility that I am dealing with something like a retroperitoneal lymphosarcoma, with pressure on or even invasion of the inferior vena cava, but my first bet is cancer of the body of the pancreas.

DR. BENJAMIN CASTLEMAN: Dr. Kranes, would you make a different diagnosis, or would you agree with Dr. Baker?

DR. ALFRED KRANES: His diagnosis seems like a very reasonable one to me.

DR. PERRY CULVER: Dr. Baker arrived at the same diagnosis that we eventually considered, but he based his reasoning on a better understanding of the possible significance of altered vascular anatomy that might have been present. Unfortunately, we disregarded the abdominal veins. This man was a very robust, jovial extrovert who appeared the picture of health and had kept his hospital roommates in a happy state. He was supposed to have lost 30 pounds of weight, but when we looked at him we could see no signs of weight loss. He had a completely negative work-up, and we wondered whether he was malingering. What finally impressed us were the facts that these pains awakened him at night and that he had weighed 190 previously but now weighed only 155 pounds. We had to believe his story of weight loss in spite of the way he looked. He also assumed a bizarre and characteristic posture whenever he had pains — that is, he lay in bed and put his foot up in the trapeze to relieve the pain. Putting these facts together with the knowledge that back or retroperitoneal pain relieved by bizarre posture in a so-called psychoneurotic patient should cause suspicion of cancer of the pancreas, we did certain tests as listed in the protocol. We placed a great deal more emphasis on these tests than Dr. Baker did, but perhaps his reasoning was more logical than ours. The fasting blood sugar of 114 mg. per 100 cc., a slightly elevated alkaline phosphatase, a slightly elevated bromsulfalein retention and a serum amylase that was just above the normal limits made us suspect disease in the pancreatic and biliary tracts. The diabetic glucose tolerance test was enough more positive objective evidence to make us all agree that a surgical exploration was indicated.

### CLINICAL DIAGNOSIS

?Carcinoma of body and tail of pancreas.

### DR. MYLES P. BAKER'S DIAGNOSIS

Carcinoma of body of pancreas.

### ANATOMICAL DIAGNOSIS

*Adenocarcinoma of pancreas, with metastasis to liver.*

### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The operation was done by Dr. Gordon A. Donaldson; he is not here, but Dr. Rodkey will tell us what was found.

DR. GRANT V. RODKEY: Dr. Donaldson found a mass approximately 10 cm. in diameter at the junction of the body and tail of the pancreas and metastatic nodular tumors in the liver; no ascites was noted.

DR. CASTLEMAN: There were several metastases to the liver, including a large one in the right lobe that was apparently not large enough to produce elevation of the diaphragm. Also, a large number of lymph nodes around the celiac axis were involved; this probably caused a great deal of pressure on the venous system in that region. A biopsy of one of the nodules in the liver showed a characteristic adenocarcinoma, consistent with a primary tumor in the body of the pancreas.

DR. RODKEY: The problem of a shooting or episodic type of pain still troubles us. I assume that it must have been because of nerve invasion in the back.

DR. CASTLEMAN: Certainly, there may have been such involvement, with so much lymph-node disease in the retroperitoneal region.

DR. RODKEY: Clinically, it sounded as though the patient were having intussusception in episodes. I think those symptoms were on a nerve basis.

DR. CULVER: I should like to take a minute to talk about the morphine-neostigmine test. Dr. Baker is right in stating that it is very hard to interpret. In certain cases of pancreatitis in which there seems to be spasm of the sphincter of Oddi, at least spasm of the pancreatic ducts, the test has helped us make the diagnosis of chronic recurrent pancreatitis unless there has been too much destruction of the pancreatic tissue. We wondered if this patient had a chronic recurrent pancreatitis and therefore did this test. I think such a test is not very helpful in trying to diagnose cancer of the pancreas.

DR. BAKER: Was the head of the pancreas involved?

DR. CASTLEMAN: No.

DR. BAKER: What happened to the patient?

DR. CULVER: He is failing very fast.

DR. JACOB LERMAN: Can you explain the eosinophils of 10 per cent?

DR. CASTLEMAN: No; was that repeated?

DR. CULVER: No.

DR. BAKER: Since the tumor did not involve the head of the pancreas, how do you account for the alkaline phosphatase elevation?

DR. CULVER: I think that represented invasion of the liver.

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## CASE 41012

### PRESENTATION OF CASE

*First admission.* A fifty-one-year-old rubber-mill worker was admitted to the hospital because of dyspnea.

The patient had been in good health until four years previously, when he noted exertional dyspnea associated with rapid heart action. The dyspnea was progressive, and in the past year walking across the factory floor caused difficulty in breathing. For the two weeks before admission the dyspnea had been severe, especially during each of the past three nights, most of which he had spent at an open window gasping for each breath. He had attempted to do some carpentry work on the day of admission, but had had to stop. His physician gave him digitalis and advised hospitalization.

The patient had never had rheumatic fever, arthritis, skin eruption, febrile illnesses or venereal disease. He had never been told that he had heart disease. Twenty-five years before admission he had served with the Marines in China for five years.

Physical examination revealed a well developed, tachypneic man. The neck veins were markedly distended. The chest was clear to percussion. Moist rales were heard at both bases. The border of the heart extended to the anterior axillary line. The apical impulse was visible in the sixth intercostal space, 12 cm. from the midsternal line. The rhythm was regular. The pulmonic second sound was much louder than the aortic. There were a Grade 2 aortic diastolic blow, best heard along the left sternal border, and a Grade 2 harsh aortic systolic murmur. A Grade 2 diastolic rumble with a presystolic crescendo and a Grade 2 systolic blow were heard at the apex. The mitral first sound was accentuated and had a snapping quality. The abdomen was normal. The deep tendon reflexes were normal. There was + pitting edema of the ankles.

The temperature was 99.2°F., the pulse 80, and the respirations 24. The blood pressure was 140 systolic, 50 diastolic.

The urine showed no abnormal features. Examination of the blood revealed a hemoglobin of 13.0 gm. The white-cell count was 9600, with 86 per cent neutrophils. The sodium, potassium, chloride, nonprotein nitrogen and carbon dioxide combining power were all within normal limits. A stool examination was negative to the guaiac test. A sputum culture revealed abundant alpha-hemolytic streptococci, moderate growth of *Neisseria catarrhalis* and a few colonies of *Staphylococcus albus*. An electrocardiogram showed a normal sinus rhythm, a PR interval of 0.14 second, a QRS interval of 0.07 second and tall R waves in Leads $V_5$ and $V_6$. The ST segments were sagging in Leads aVL, $V_5$ and $V_6$; the T waves were low and biphasic, and the P waves were broad and notched. A tracing taken on the next day revealed no significant changes. An x-ray film of the chest showed an enlarged heart, with enlargement of the left but not of the right ventricle (Fig. 1). The cardiothoracic ratio was 16:30. There were moderate pulmonary congestion and ill defined areas of increased density over much of the right lung. Multiple large blebs were present in the right lung, and free fluid was noted in the right pleural cavity.

The patient was given oxygen by mask, 0.8 mg. of Cedilanid intravenously, 2 cc. of Mercuhydrin intramuscularly and 600,000 units of aqueous penicillin. During the next eleven days in the hospital he improved on bed rest, a low-salt diet, penicillin, digitoxin and Mercuhydrin. An x-ray film of the chest showed less congestion, but strands of increased density were still noted throughout both lungs. He was discharged very much improved on the eleventh hospital day.

*Final admission* (two weeks later because of severe dyspnea). His wife stated that he had been doing fairly well until three days previously, when he felt cool in the morning, and that evening he felt flushed. The following morning he began to vomit after breakfast, and this continued for the next two days. Two days before admission he had a shaking chill followed by sweating. His family physician discontinued digitalis and potassium iodide and began treatment with erythromycin. He continued to be severely dyspneic, with retching and anorexia on the day before admission and that night slept very poorly. On the day of admission he had paroxysms of coughing and retching.

FIGURE 1. *Posteroanterior Film of the Chest, Four Days after the Initial Examination.*

*The lungs are free of edema; there is evidence of marked pulmonary emphysema, particularly on the right. The blebs are not well seen in the photograph.*

Physical examination revealed an acutely and desperately ill, dyspneic, cyanotic man who was unable to speak more than a few words because of severe dyspnea. The pupils were small, round and equal and reacted well to accommodation but not to light. The scleras were injected but not icteric. The neck veins were not distended. The lungs were clear to percussion, and an occasional distant wheeze was heard. There was a Grade 2 to-and-fro murmur at the apex that could not be delineated into systolic and diastolic murmurs. No murmurs were heard at the base. The pulmonic second sound was louder than the aortic. The abdomen was normal.

The temperature was 103°F., the pulse 120, and the respirations 40. The blood pressure was 110 systolic, 60 diastolic.

The urine gave a ++ test for albumin; the sediment contained many granular casts per high-power field but no white cells or red cells. Examination of the blood revealed a hemoglobin of 13 gm. per 100 cc. and a white-cell count of 16,800. The sodium was 120 milliequiv., the potassium 6.5 milliequiv., the chloride 92 milliequiv., and the carbon dioxide 17 milliequiv. per liter. The blood pH was 7.39. An x-ray film of the chest showed patchy areas of increased density throughout both lung fields, especially in both upper lobes (Fig. 2). The emphysematous blebs were more apparent in contrast to adjacent consolidation. The heart shadow was unchanged.

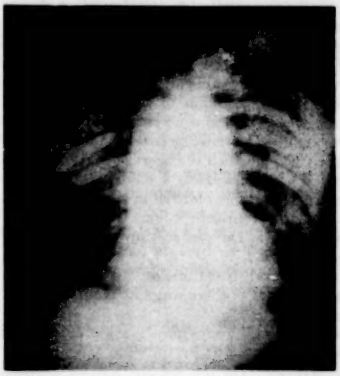

FIGURE 2. *Anteroposterior View of the Chest Shortly before Death, Showing Evidence of Massive Pulmonary Edema Bilaterally.*

*The heart and aorta are magnified because of the manner in which the film was exposed.*

The patient was immediately given oxygen under positive pressure and Digalin. He preferred lying back at a 20° angle to sitting up. Suddenly, about ten hours after admission, he became more dyspneic and called out that he could not breathe. The lungs were full of coarse rales. The pulse was regular at a rate of about 150. He was given 0.4 mg. of Cedilanid intravenously, tourniquets were applied, and he was placed in a sitting position. He died within a few minutes. Terminally, the neck veins, which had previously been flat, became distended.

## Differential Diagnosis

Dr. Gordon S. Myers*: First, I shall ask Dr. Hanelin to show the x-ray films because I think that they may help me discuss the problem intelligently.

Dr. Joseph Hanelin: The initial film indicates a great deal of change in the lung fields that is seen on all the subsequent films and is better demonstrated after the initial congestion has cleared. The heart is definitely enlarged, and I shall say more about its configuration in the later examinations. There are large zones of density in both lungs consistent with pulmonary edema. When the congestive changes have largely cleared (Fig. 1), about four days later, there are huge blebs visible in the lungs, particularly on the right side. There are scattered strandlike densities in both lung fields and also a fair number of small nodular lesions. These changes are consistent with chronic pulmonary disease. What the shape of the heart might indicate about individual chamber enlargement is extremely difficult or impossible to say. I suspect that in addition to hypertrophy of the left ventricle there may also be considerable enlargement of the right. This is suggested by the right anterior oblique view, in which the heart shows anterior prominence. Two weeks later, a day or so before death, there are again large blotches of density in both lungs that probably represent edema (Fig. 2).

Dr. Myers: Do you see any calcification in the ascending aorta?

Dr. Hanelin: No; I do not.

Dr. Myers: Is there any enlargement of the left atrium?

Dr. Hanelin: There may be slight enlargement of the left atrium.

Dr. Myers: Do you see any sign of intracardiac calcification?

Dr. Hanelin: No; I cannot see any.

Dr. Myers: Do you think any of the lesions in the lung are consistent with pulmonary emboli?

Dr. Hanelin: I cannot be certain of any areas of infarction. One might wonder in the last film whether some of the densities were due to infarcts.

Dr. Myers: Could some of the strandlike areas of fibrosis represent old infarcts?

Dr. Hanelin: That is possible, but the picture is not too characteristic.

Dr. Myers: After the congestion has cleared up, can you see any areas of emphysema and fibrosis?

Dr. Hanelin: There is a great deal of emphysema and many areas of fibrosis.

Dr. Myers: The initial history and physical examination are quite consistent with rheumatic heart disease, aortic and mitral disease and congestive heart failure. This patient had progressive dyspnea, beginning at about the age of forty-seven. The fact that he had no past history of rheumatic fever or rheumatic heart disease is not too disturbing because such a history is frequently absent in patients with proved rheumatic heart disease. Initially, when he came into the hospital he had dyspnea, distention of the neck veins, rales at the lung bases, cardiac enlargement, accentuation of the pulmonic second and mitral first sounds and double murmurs at the apex and aortic areas. The blood pressure of 140 systolic, 50 diastolic, indicates an important degree of aortic regurgitation, and the electrocardiogram points decisively to hypertrophy of the left ventricle. Evidently, at the time of the first admission, he was thought to have congestive heart failure and probably some pulmonary infection since he was given penicillin. In addition he was later given potassium iodide so that the physicians who took care of him must have thought he had chronic pulmonary disease.

It must have been surprising at the time of the second admission, when he was cyanotic and extremely dyspneic, with fever and a rapid pulse, to find no definite evidence of congestive heart failure on physical examination: the neck veins were said to be normal, and there were no rales in the lungs. Nevertheless, the x-ray film of the chest taken at that time indicated a considerable degree of congestion in the lungs. It is not too uncommon to see clear evidence of marked pulmonary congestion in x-ray films and to hear very little or nothing by auscultation.

One wonders about the change of the auscultatory findings at the time of the second admission. Apparently, no murmurs were heard at the base, and there was some kind of to-and-fro murmur, which was vaguely described, that could not be delineated into a definite systolic and diastolic murmur. Perhaps this was a pleuropericardial friction rub. The observation that the murmurs were not well heard at that time could be explained by the fact that he was so desperately ill, with a very rapid heart rate. Under such circumstances, murmurs that have previously been quite obvious disappear or become very difficult to detect.

The white-cell count had risen to 16,800, which makes one think of infection or infarction. The fall in the sodium chloride could have been due to the low-salt diet, diuretics and vomiting, but the fall in the carbon dioxide and rise in the potassium make one wonder about renal impairment. If I knew the specific gravity of the urine and nonprotein nitrogen, it might be of some help.

Dr. Benjamin Castleman: There was not enough urine on which to test the specific gravity during the final admission. The patient was in for only two days so there was enough time to determine the extraordinary electrolyte values but not the nonprotein nitrogen!

Dr. Myers: It occurred to me that he could have had emboli to the kidneys, with multiple infarcts, but there was no clear evidence of this, in view of the facts that he did not complain of pain, examination of the abdomen was negative and the urine contained no red cells. I suspect that the specific gravity was

*Assistant physician, Massachusetts General Hospital.

high and that this picture represented prerenal azotemia, with further electrolyte imbalance due to previous therapy and vomiting.

One must always have a high index of suspicion in discussing cases in these conferences, but I can be reasonably sure that the patient had aortic regurgitation: there was a perfectly reasonable murmur for it, the electrocardiogram indicated left-ventricle hypertrophy and the pulse pressure was wide. Was the aortic regurgitation due to rheumatic heart disease or some other defect? Were the Wassermann and Hinton tests negative?

DR. CASTLEMAN: None were done.

DR. MYERS: So that we do not have a serologic report on this patient. However, there was no previous history of syphilis, there was no calcification of the ascending aorta, and the reflexes were said to be normal. The only confusing detail is the fact that one physician noted that the pupils were fixed to light and reacted to accommodation. I do not believe that this patient had aortic regurgitation on the basis of syphilitic heart disease. Although one can have an Austin-Flint murmur in the absence of mitral disease, giving rise to a presystolic murmur at the apex, the fact that he had a very loud mitral first sound and broad, notched P waves in the electrocardiogram leads me to believe mitral disease was also present.

DR. CASTLEMAN: Why does the electrocardiogram lead you to suggest mitral disease?

DR. MYERS: Ordinarily, patients who have aortic regurgitation and hypertrophy of the left ventricle, with or without dilatation of the left atrium, are not so likely to show broad, notched P waves, usually indicating some involvement of the atrium, often by coronary-artery disease or rheumatic heart disease.

DR. CASTLEMAN: That is due to the involvement of the atrium itself, a myocarditis?

DR. MYERS: Presumably, the atrium itself is the site of myocarditis or fibrosis. This does not exclude the possibility that the patient had only aortic regurgitation, but that seems to me considerably less likely.

The next question is, What was going on in the lung? The x-ray films showed emphysematous blebs and areas of increased fibrosis. The patient was a rubber-mill worker; Dr. Harriet L. Hardy tells me that such workers are exposed to talc and may therefore be subject to pulmonary fibrosis, which may ultimately cause cor pulmonale. Certainly, there is no definite evidence of cor pulmonale here; if there was any it must have been a very minor part of the picture.

Could there have been pulmonary emboli? I did not have the advantage of seeing the x-ray films when I first read the protocol, and I must say that I was suspicious of multiple pulmonary emboli. To be sure, pleural pain and hemoptysis were not present, but they are not invariable symptoms of pulmonary infarcts. Pulmonary emboli occur in roughly 50 per cent of patients with rheumatic heart disease and mitral stenosis who die in congestive heart failure. That makes the possibility of this complication a very real one. Nothing was said about the legs, but many patients with phlebothrombosis show nothing in the legs. Furthermore, the electrocardiogram demonstrates changes that point to pulmonary emboli in only about 10 per cent of cases. Pulmonary emboli might account for some of the x-ray findings, the clinical course of the patient with increasing congestive heart failure and the fever and leukocytosis shortly before death.

It is true, of course, that chills and abdominal symptoms, with nausea and vomiting, are quite uncommon with infarcts; therefore, bronchopneumonia may have complicated the picture. Other unlikely complications, which we do not have time to discuss in detail, I shall just mention: active rheumatic fever, subacute bacterial endocarditis complicating myocardial infarction, ball-valve thrombus in the left atrium and mesenteric or renal infarcts. None of these can I diagnose on the basis of the evidence at hand.

I shall have to conclude that this patient had rheumatic heart disease, predominantly of the aortic valve, with regurgitation and stenosis, but probably with some mitral stenosis and regurgitation as well, and that he had chronic pulmonary disease. Possibly the chronic pulmonary fibrosis was on the basis of the industrial exposure to talc. I think it likely that he had pulmonary emboli, at least at the time of the final illness, with or without bronchopneumonia.

A PHYSICIAN: Was there any enlargement of the left atrium?

DR. HANELIN: The evidence for it is slight. I do not think it is a large chamber. There is a slight posterior bulge of the esophagus at the level of the atrium that might result from some increase in its size. It is not of the size usually associated with mitral stenosis. In the presence of failure of the left ventricle there may be some increase in the size of the atrium.

DR. LEWIS KANE: It interests me that in the last admission he had a carbon dioxide of 17 milliequiv. per liter and was given oxygen, and that the terminal episode occurred shortly thereafter.

DR. CASTLEMAN: You mean that there may have been some oxygen intoxication?

DR. MYERS: I think it is worth pointing out that patients with pulmonary disease who get into trouble with oxygen inhalation do so because of a rising carbon dioxide tension. Usually, they are in acidosis with an elevated carbon dioxide, and become more or less stuporous and then comatose and finally may die. That was not the picture here. The patient continued to be very dyspneic and finally died with a very severe episode of shortness of breath. I do not believe that was the mechanism of his death.

DR. KANE: The carbon dioxide serves as a stimulus for respiration. When the oxygen is administered and the carbon dioxide is decreased, the stimulus would be decreased accordingly.

DR. MYERS: That apparently did not occur here. This patient was breathing very rapidly up to the time of death.

### CLINICAL DIAGNOSES

Rheumatic heart disease, with aortic and mitral regurgitation and stenosis.
Chronic pulmonary fibrosis and emphysema.

### DR. GORDON S. MYERS'S DIAGNOSES

Rheumatic heart disease, with aortic and mitral stenosis and regurgitation.
Chronic pulmonary fibrosis.
Pulmonary emboli, ?with bronchopneumonia.

### ANATOMICAL DIAGNOSES

*Syphilitic heart disease, with aortitis, aneurysmal dilatation of ascending aorta and narrowing of right coronary ostium.*
*Pulmonary fibrosis, bilateral.*
*Pulmonary emphysema, bilateral.*
Hydrothorax, bilateral.
Pulmonary edema.
Bronchopneumonia.

### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At the time of autopsy the infiltration of the lungs proved to be pulmonary edema and bronchopneumonia. We were unable to find any infarcts. We did find pleural fluid, — 800 cc. on the left and 500 cc. on the right, — which seems surprising, for the costophrenic angles look fairly sharp on the x-ray films.

DR. HANELIN: Do you know the interval between the date of the film and death?

DR. J. R. PETRANEK: The last films were taken four hours before death.

DR. HANELIN: I should think that this much fluid would have been shown; most of it must have developed after the film was taken.

DR. CASTLEMAN: The underlying disease in the lung was very severe pulmonary emphysema, with huge blebs and a great deal of fibrosis. Certainly, the pulmonary reserve was very small so that the patient was likely to go into heart failure very easily. The heart was large, weighing almost 500 gm.; most of the increase was of the left chamber. The right ventricle measured only 4 mm., which, with that degree of emphysema and fibrosis, does not represent very much enlargement; there was certainly not a great deal of right-sided heart failure. The valve lesion was entirely aortic and showed as classic a picture of syphilitic aortitis as we ever see. In retrospect, Dr. Hanelin, is this ascending aorta on the x-ray film a little wide?

DR. HANELIN: Not particularly so.

DR. CASTLEMAN: It was.

DR. HANELIN: It does not look it.

DR. CASTLEMAN: There was a definite dilatation of the ascending aorta, with the classic tree barking and wrinkling of the intima but without calcification. The aortic cusps were separated at the commissures up to 2 and 3 mm. in places, allowing for a free aortic regurgitation, which was proved by perfusion of the heart post mortem by Dr. Fairfield Goodale, Jr. Further confirmation was a small area of connective tissue in the form of a cusp on the endocardium of the ventricle below the valve — a teleologic attempt to form a fourth cusp to prevent further regurgitation! There was no disease of the mitral valve so that I think the murmur was an Austin-Flint one.

It is unfortunate that a blood Hinton or Wassermann test had not been done. Since we now see so little syphilis we often find this omission.

DR. MYERS: Was there anything abnormal in the abdomen?

DR. CASTLEMAN: No.

Microscopical examination of the ascending aorta revealed some intimal sclerosis, with a little calcification, and the medial degeneration and adventitial cellular infiltration characteristic of syphilis.

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Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
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THE NEW HAMPSHIRE MEDICAL SOCIETY
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## HAPPY NEW YEAR

THE year 1954 was the the healthiest on record for the American people, according to the indefatigable statisticians of the Metropolitan Life Insurance Company. This record has been achieved despite a rising consumption of tobacco until recently, an increase in the automotive potentials of destruction, more — and more slippery — bathtubs and various ancestral voices prophesying war.

The fact of the national death rate having dropped to its all-time low of 9.2 per 1000 population, or 5 per cent less than that of the previous year, — when an all-time low had also been established, — seems no less admirable when one is confronted with the prediction that a new all-time low may also be established in 1955. But more of that some months anon.

The country's current wave of all-time low mortality rates has resulted from a number of circumstances. There has been an absence of any major outbreaks of respiratory disease, and the death rate from tuberculosis has continued to fall — by approximately 20 per cent in a single year. The death rates from poliomyelitis, measles and whooping cough have remained low although the number of cases of all these diseases has risen. The rate from diabetes has dropped, and so, *mirabile dictu*, has that from all types of accidents. The homicide rate, on the other hand, has risen. The suicide rate has remained at a level despite the suggestion made to the inquisitive scientist by James Thurber's lemming, which, when told that it was a mystery why lemmings rushed into the ocean and were drowned retorted that the real mystery was why human beings did not. Infant and maternal mortality rates, perhaps anticlimactically, have continued to decline.

The prospect that apparently confronts a prosperous and health-conscious nation seems encouraging. It must be remembered, however, that what goes up must come down and sometimes the reverse is true. For lower death rates now must inevitably be succeeded by higher ones eventually, when time catches up with a fortunate generation that has been given a longer lease of life than was ever before experienced. So far as present knowledge goes, individual man is born but once and dies but once, and modern social and political standards have decreed that both these events must be recorded.

An evaluation of the beneficial results of today's health-bent efforts seems to indicate that decreased infant mortality rates and a lowering of those from various avoidable as well as from all unpleasant causes are a desideratum; and certainly most important of all would be a high level of physical and mental health while life persists.

What might be hoped for, then, as the death rate returns to an irreducible minimum in relation to the number of births would be a healthy race, a reason-

ably prolonged and happy life, whatever these qualifications mean, and a spectacular relative increase in the rate of demise from so-called heart disease.

## THE HOUSE OF DELEGATES

THE House of Delegates of the American Medical Association and its reference committees constitute a truly representative and democratic body, as anyone who has attended their deliberations can testify. It is difficult for such a body to form decisive opinions and policies. What pleases the right wing seldom satisfies the left.

Thus, at the clinical meeting in Miami, November 29 to December 2, 1954, authoritative pronouncements on such controversial subjects as the proper extent of veterans' medical care, President Eisenhower's continued backing of federal reinsurance of voluntary health coverage, a revived Bricker resolution, federal aid to medical schools and the relations between osteopathy and medicine were either deferred, pending more careful study, or left to the subsequent discretion of the Board of Trustees, who will speak as the occasion arises.

The trustees appointed a committee to discuss veterans' care with a committee representing the American Legion, after an invitation by Commander Seaborn Collins, whose temperate remarks seemed to be sympathetically received.

The delegates listened politely to a defense of federal reinsurance by Secretary Oveta Culp Hobby, but applauded (perhaps with less tact than vigor) a devastating attack upon the plan made by an insurance executive.

The *Principles of Medical Ethics* were revised to permit physicians to patent surgical instruments, appliances and medicines, and to copyright publications, methods and procedures. Only the use of such products or the receipt of remuneration from them to "retard research or restrict benefits derivable therefrom" is now unethical.

The report of the *ad hoc* Committee on Internships was merely referred to the Council on Medical Education and Hospitals for future study and guidance. The House of Delegates recorded itself as being in complete accord with the Board of Trustees and its council on national defense that the "doctor-draft" law should not be extended after June 30, 1955, and confidence was expressed in their ability to handle any new situation that may develop in this highly complex and involved problem.

Dr. Karl B. Pace, of Greenville, North Carolina, was chosen General Practitioner of the Year. Philadelphia was selected as the place for the 1957 clinical meeting, which will be held in Boston in 1955 and in Seattle in 1956.

## GIFTS WITHOUT GIVERS

THE *Journal*, in the issue of October 29, 1953, published a brief account of the beginning and the subsequent history of the Massachusetts Medical Benevolent Society, now nearly ninety-nine years of age. As was noted at that time, the Society was the result of a meeting of certain members of the Boston Medical Book Club, held in December, 1856. These physicians, disturbed at the straitened circumstances of some of their superannuated colleagues and their families, and acting on the sound principle that benevolence should begin at home, then and there organized the Society, which had its first full-fledged meeting on March 19, 1859, and was incorporated fourteen years later.

In the heyday of its youth, when possibly man's inhumanity to man was in some ways a less conspicuous reality than it appears to be today, the Society had a large membership in and around Boston, and from its dues, however small, and various donations and bequests a modest endowment was accumulated. The principal thus gradually acquired reached its maximum of about $100,000 within recent years, and the income from interest and other sources, not including various monies received from the Massachusetts Medical Society, has gone but little over $6,000 a year.

To aid this cause so very close to home, the Massachusetts Medical Society in 1948 formed its Committee on Benevolence and established a fund, which has been allocated from time to time to various needy recipients, through the agency of the Massachusetts Medical Benevolent Society.

Old philanthropies, however, as new and more spectacular ones thrust their way to the center of the stage, tend to be forgotten; the ninety-eighth annual meeting of the Society held in December, 1954, disclosed a roster of only 34 members now paying the annual dues of $5, and 99 life members exempt from dues and assessments. The gift without the giver is said to be bare, but despite the numerical loss in the Society's membership 22 beneficiaries have been aided during the year in the amount of $9071 at an administrative expense of only $171.89.

The Massachusetts Medical Benevolent Society represents a philanthropy that should reach the hearts and minds of Massachusetts physicians by a shorter route than could any other form of benevolence. A membership of only 133 out of the 7000 eligible fellows of the Massachusetts Medical Society seems a shocking fact with which the Benevolent Society must face its approaching hundredth anniversary. An enrollment of a thousand physicians in an organization dedicated to the relief of their needy colleagues is hardly too much to expect. Surely all that is necessary to achieve a tenfold increase is an

awareness of the need and a knowledge of the fact that a check for $5, payable to the Massachusetts Medical Benevolent Society, and sent to the treasurer, Dr. Charles C. Lund, 319 Longwood Avenue, Boston 15, Massachusetts, will enroll one as a member.

## "ROADS TO BETTER NURSING"

THE second annual meeting of the Massachusetts League for Nursing, held at the New Ocean House, Swampscott, October 25 and 26, was stimulating, refreshing and challenging. It introduced enough ideas for further consideration to occupy the membership for more than a year.

The program demonstrated the philosophy of the National League for Nursing, the co-operation of nurses on all levels of responsibility and of preparation, examining together their common problems aided by colleagues from allied fields and by interested laymen, all contributing to the theme, "Roads to Better Nursing." As a large part of the program nine special-interest groups discussed current nursing problems. These included the expanding role of the nurse in research, in cancer nursing, in operating-room nursing, in psychiatric nursing and as a consultant in nursing-service administration; the provision of a better family health service; improvement of nursing-service administration; enrichment or shortening of the diploma program; and juvenile delinquency — a community responsibility in maternal and child health programs. A variety of methods of stimulating intelligent discussion were used. Some topics were introduced by papers, some by panels, and still others by controversial questions or ideas.

Dr. Hugh Leavell, professor of public-health practice, Harvard School of Public Health, demonstrated the common elements in world health needs and the sources of knowledge from which public-health science is derived. Tracing the natural history of disease, he showed that there are five levels of prevention and that the objectives of curative and preventive medicine should be the same. Responsibility rests on both hospital and community to plan nursing care in relation to all five levels. Preparation for nursing along with other health disciplines necessitates broad planning to utilize educational and physical resources economically and effectively. He further emphasized the concept of regionalization and the expanding role of the universities in the education of personnel equipped for this widening role of organized public-health and hospital service.

Mrs. Welles Belin, a lay member from the Visiting Nursing Association of Scranton, Pennsylvania, gave an address, based on the ten points expressed by Michael Davis, entitled "The Citizen's Contribution to Nursing." She outlined a plan of action that could channel over a five-year period the energy and interest of laymen in promoting the objectives of the Massachusetts League for Nursing.

Esther Lucile Brown, Ph.D., of the Russell Sage Foundation, introduced a challenge to nursing in her address, "The Social Sciences and Patient Care."

With its sights on such objectives, the profession of nursing has exchanged its somewhat unflattering characterization as a so-called "ancillary" service (from *ancilla* — a female servant) for full partnership in the great enterprise of guaranteeing to human beings reasonable conditions for the pursuit of health and happiness.

Suffolk District Medical Society. — *We are advised that, on account of illness in Dr. Warren's family, the social meeting of the Suffolk District Medical Society will be omitted for this month.*
Boston M. & S. J., *Jan. 10, 1855*

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

BARRETT — Raymond L. Barrett, M.D., of Longmeadow, died on December 10. He was in his sixty-first year.

Dr. Barrett received his degree from Columbia University College of Physicians and Surgeons in 1921. He was a former councilor of the Massachusetts Medical Society and a member of the staffs of the Springfield, Springfield Health Department and Cooley Dickinson hospitals. He was a fellow of the American College of Physicians, the American Medical Association and the Springfield Academy of Medicine and a member of the Osler Club.

He is survived by his widow, two sons, three brothers, three sisters and three grandchildren.

JONES — Thomas Duckett Jones, M.D., of New York, died on November 22. He was in his fifty-sixth year.

Dr. Jones received his degree from the University of Virginia Department of Medicine in 1923. He was medical director of the Helen Hay Whitney Foundation, New York City, a member of the faculty of Harvard Medical School and the staffs of the Massachusetts General Hospital and the House of the Good Samaritan, Boston, vice-president of the American Heart Association and chairman of its Council on Rheumatic Fever, president, the Protein Foundation, president-elect, National Health Council, and chairman, Committee on Plasma Fractionation and Related Processes, Laboratory of Physical Chemistry, Harvard University. He was a fellow of the American Medical Association and a member of the Association of American Physicians, American Society for Clinical Investigation and the American Clinical and Climatological Association.

He is survived by three sisters and a brother.

SALMON — Charles A. Salmon, M.D., of Worcester, died on December 9. He was in his sixty-fifth year.

Dr. Salmon received his degree from Tufts College Medical School in 1917. He was formerly public-school physician and in charge of the rehabilitation clinic for war veterans in Worcester.

He is survived by a sister and three brothers.

SIMON — Arthur L. Simon, M.D., of Lawrence, died on November 23. He was in his seventy-fourth year.

Dr. Simon received his degree from Tufts College Medical School in 1905. He was a member of the associate medical staff of the Lawrence General Hospital.

He is survived by two daughters and a brother.

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WEBBER — Wolfert G. Webber, M.D., of Amherst, died on December 9. He was in his sixty-sixth year.

Dr. Webber received his degree from Harvard Medical School in 1913. He was formerly assistant commissioner, Massachusetts Department of Public Health, and epidemiologist, City of Boston. He was a fellow of the American Medical Association.

He is survived by his widow and two sons.

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# NONCLINICAL NOTES

## NEW ENGLAND SINAI HOSPITAL

The New England Sinai Hospital, at 215 Forest Hills Street, Jamaica Plain, was dedicated on December 19. This hospital is an outgrowth of the Jewish Tuberculosis Sanatorium of New England, Rutland, Massachusetts, and will continue the same policies of treating patients on a nonsectarian and mainly charitable basis.

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# NOTICES

## ANNOUNCEMENT

Dr. H. A. Nissen announces the removal of his office from 99 Commonwealth Avenue to 205 Beacon Street, Boston, for the practice of internal medicine with special reference to arthritis.

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## USE OF TELEVISION IN POSTGRADUATE MEDICAL EDUCATION

The Council on Medical Education and Hospitals of the American Medical Association will present a program on the subject "Potential Use of Television in Postgraduate Medical Education" in the ballroom, Palmer House, Chicago, on February 5.

It is expected that this will be the first of a series of annual workshop-type conferences on a particular aspect of postgraduate medical education.

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## FRANCIS AMORY SEPTENNIAL PRIZE

In compliance with the terms of a gift under the will of Francis Amory, the American Academy of Arts and Sciences offers a substantial prize for outstanding work on the alleviation or cure of diseases affecting the human reproductive organs, in particular those of men. The work may be instrumental technology, operative procedure, clinical or laboratory research, or a technical treatise. No informal applications and no essays or treatises from candidates are desired, but nominations, supported by statements of qualifications regarding work consummated between November 10, 1947, and November 10, 1954, will be given careful consideration. Nominations should be addressed to the American Academy of Arts and Sciences, 28 Newbury Street, Boston 16, Massachusetts.

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## SOCIETY MEETINGS AND CONFERENCES

JANUARY–APRIL. Postgraduate Medical Institute. Page 451, issue of September 9.

JANUARY–MAY. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

JANUARY 6–26. Consultation Clinics for Crippled Children in Massachusetts. Page 1074, issue of December 23.

JANUARY 7–MARCH 25. Postgraduate Course in Occupational Medicine. Page 922, issue of November 25.

JANUARY 8–MAY 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.

JANUARY 10–15. Course in Care of Atomic Casualties. Page 285, issue of August 12.

JANUARY 10–MAY 9. Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

JANUARY 17. Hartford Medical Society. Page 496, issue of September 16.

JANUARY 18, FEBRUARY 1 and 15. New England Deaconess Hospital Lectures. Page 993, issue of December 9.

FEBRUARY 4. New England Society of Anesthesiologists. Page 1075, issue of December 23.

FEBRUARY 4 and APRIL 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.

FEBRUARY 7–9. McIntyre-Saranac Conference. Page 410, issue of September 2.

FEBRUARY 11–25. Pan-American Academy of General Practice. Page 496, issue of September 16.

FEBRUARY 26 and 27. Mid-Winter Radiologic Conference. Page 1076, issue of December 23.

FEBRUARY 28–MARCH 2. American Orthopsychiatric Association. Page 994, issue of December 9.

MARCH 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.

MARCH 23–26. International Academy of Proctology. Page 876, issue of November 18.

APRIL 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.

MAY 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.

JUNE 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.

JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

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## CALENDAR FOR THE WEEK BEGINNING THURSDAY, JANUARY 13

**THURSDAY, JANUARY 13**

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Multiple Myeloma. Dr. Eugene Sullivan. Regional Office of the Veterans Administration, Conference Room, 4th floor, 17 Court Street, Boston.

*11:00 a.m. Thoracic Conference. Further Report on the Results of Surgical Treatment of Mitral Stenosis. Dr. Laurence B. Ellis. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

12:00 m.–1:00 p.m. Staff Conference. The Patterns of Neuronal Assemblies and Their Meaning in the Biological Organization of Behavior. Dr. Paul I. Yakovlev. Stearns Auditorium, New England Center Hospital.

*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

*4:30–5:30 p.m. Physiological Basis for Treatment of Diabetic Acidosis. Dr. Samuel Bolan. Auditorium, Nurses' Home, Cambridge City Hospital.

5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

**FRIDAY, JANUARY 14**

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30 a.m. Cardiac Physiology. Dr. Henry D. Stebbins. Salem Hospital, 81 Highland Avenue, Salem.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

*(Concluded on page xxix)*